ACTUAL AND PRESCRIBED ENERGY AND PROTEIN INTAKES FOR VERY LOW BIRTH WEIGHT INFANTS: AN OBSERVATIONAL STUDY

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To my very special friend, Bob, who provided encouragement and support. To my loving and supportive family, Joanah and Darwin Bodero, Heather and Richard Morris, and Paul Scanga, who provided encouragement all the way.

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ABSTRACT

Deborah Marie Abel

ACTUAL AND PRESCRIBED ENERGY AND PROTEIN INTAKES FOR VERY LOW BIRTH WEIGHT INFANTS: AN OBSERVATIONAL STUDY

Objectives: To determine (1) whether prescribed and delivered energy and protein intakes during the first two weeks of life met Ziegler's estimated requirements for Very Low Birth Weight (VLBW) infants, (2) if actual energy during the first week of life correlated with time to regain birth weight and reach full enteral nutrition (EN) defined as 100 kcal/kg/day, (3) if growth velocity from time to reach full EN to 36 weeks' postmenstrual age (PMA) met Ziegler's estimated fetal growth velocity (16 g/kg/day), and (4) growth outcomes at 36 weeks' PMA.

Study design: Observational study of feeding, early nutrition and early growth of 40 VLBW infants ≤ 30 weeks GA at birth in three newborn intensive care units NICUs.

Results: During the first week of life, the percentages of prescribed and delivered energy (69% [65 kcal/kg/day]) and protein (89% [3.1 g/kg/day]) were significantly less than theoretical estimated requirements. Delivered intakes were 15% less than prescribed because of numerous interruptions in delivery and medical complications. During the second week, the delivered intakes of energy (90% [86 kcal/kg/day]) and protein (102% [3.5 g/kg/day]) improved although the differences between prescribed and delivered were consistently 15%. Energy but not protein intake during the first week was significantly related to time to reach full EN. Neither energy nor protein intake significantly correlated with days to return to birth weight. The average growth velocity from the age that full EN was attained to 36 weeks' PMA (15 g/kg/day) was significantly less than the theoretical estimated fetal growth velocity (16 g/kg/day) (p<0.03). A difference of 1 g/kg/day represents a total deficit of 42 - 54 grams over the course of a month. At 36 weeks' PMA, 53% of the VLBW infants had

extrauterine growth restriction, or EUGR (<10th percentile) on the Fenton growth grid and 34% had EUGR on the Lubchenco growth grid.

Conclusions: The delivered nutrient intakes were consistently less than 15% of the prescribed intakes. Growth velocity between the age when full EN was achieved and 36 weeks' PMA was 6.7% lower than Ziegler's estimate. One-third to one-half of the infants have EUGR at 36 weeks' PMA.

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LIST OF ABBREVIATIONS

American Academy of Pediatrics	AAP
Amino Acids	AA
Actual/delivered Nutrition	A/D
Day of Life	DOL
Enteral Nutrition	EN
Extrauterine Growth Restriction	EUGR
Extremely Low Birth Weight	ELBW
Gestational Age	GA
Grams per kilogram per day	g/kg/day
Kilocalories per kilogram per day	kcal/kg/day
Newborn Intensive Care Unit	NICU
Parenteral Nutrition	PN
Prescribed/intended Nutrition	P/I
Postmenstrual Age	PMA
Very Low Birth Weight	VLBW

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CHAPTER 1: THE PROBLEM

1. Introduction/Background

The United States ranks 28th out of 32 countries for infant mortality (1), of which 36 percent is attributed to premature birth. Premature birth, which occurs in 1 out of 8 births, costs the United States more than $26 billion annually (1). Not only is premature birth a leading cause of newborn death but it also is a leading cause of lifelong health problems including chronic lung disease, visual and hearing loss and neurodevelopmental impairment (2 - 11). Now more than ever, modern medical practices are saving the lives of infants considered very low birth weight (VLBW) (< 1500 g, < 34 weeks postmenstrual age). For example, VLBW survival improved with the widespread use of surfactant agents, maternal corticosteroids and advancement in neonatal technology (12 - 13). Unfortunately, in the zeal to save lives and keep the infants breathing, early nutrition may be overlooked and its significance underestimated.

Premature infants have unique nutritional needs, because up to 17 weeks of their final growth occurs outside of the womb rather than intrauterine. This is the period when rapid, important growth and maturity of organ systems occurs. Emerging evidence suggests that early growth failure from inadequate nutrition in VLBW infants has long lasting effects, such as pulmonary and neurodevelopmental disabilities at older ages (3, 7, 12, and 14).

Two methods for determining nutrient requirements for premature infants are the factorial method and the empirical method (15). Ziegler describes the factorial method as using the fetal model to develop energy and protein requirements; whereas the empirical method systematically varies the energy and/or protein intakes while using growth and/or nitrogen balance as outcome measures (15). Ziegler's theoretical estimated requirements for energy and protein using the factorial method for both parenteral nutrition (PN) and enteral nutrition (EN) needs are well known and are used

as the clinical guideline in newborn intensive care units (NICU) across the country (15 - 22). The factorial method does not take into account the need to accomplish "catch-up" growth for VLBW infants.

Even when feeding protocols are followed, it has been difficult to follow and evaluate both short-term and long-term outcomes. Unless there is a way to easily monitor nutritional intake and growth progress, the best practices cannot be elucidated. In addition, failure to grow at appropriate rates in the NICU potentially impacts the length of hospitalization and associated costs that range from $6,000 to $12,000 per day for VLBW infants. Over the last decade, neonatologists have established that early delivery of protein and energy, as early as the day of birth, impacts long-term nutrition and growth outcomes (14 and 23 - 25).

This research evaluated prescribed/intended (P/I) (physician orders) and actual/delivered (A/D) (actual infant intake) energy and protein relative to Ziegler's theoretical estimated nutrient requirements for VLBW infants during the first two weeks of life, barriers to optimal nutrient delivery in the first two weeks postnatal and correlation to growth milestones. The growth milestones are day of life (DOL) return to birth weight, DOL to reach 100% of full enteral nutrition (EN) defined as 100 ±10 kcal/kg/day and growth percentiles at 36 weeks of postmenstrual age (PMA).

2. Statement of the Problem

VLBW infants experience postnatal growth failure (2, 4, 5, 7, 16 - 19, 21, and 26 - 35). When an infant's weight is less than the 10th percentile for gestational age (GA) at 36 weeks' PMA, it is termed growth failure (33). In a study performed by the clinical research centers participating in the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network in 1995 - 1996, growth failure in premature infants was documented in 99% and 97% of those with birth weights < 500 g and < 1000 g, respectively (33). Incidences of extrauterine growth restriction (EUGR), a

decrease in weight for gestational age between birth and hospital discharge, have been reduced during the last 15 years because of the increased awareness and knowledge of the importance of early initiation of PN, specifically protein. Many NICU nurseries now deliver a stock amino acid solution only a few hours after birth. Yet, even with the many advances in our nutrition knowledge, delivery of postnatal energy, protein and nutrients are deficient and growth outcomes at discharge and beyond are still a major concern for clinicians and researchers (3, 5, and 36 - 39).

Emerging evidence suggests that nutritional deficits in VLBW infants create long lasting pulmonary and neurodevelopmental disabilities (2, 3, 14, 16, and 25). These deficits are difficult to reverse and tend to be self-perpetuating. For example, significantly lower cognitive development scores and smaller head circumferences were found at 7 years of age for VLBW neonates who had lower protein intakes (1 - 2 g/kg/day vs. 3 - 4 g/kg/day) during the first 5 days after birth (40). Subnormal head circumferences in VLBW infants correlated with neonatal survival and learning/behavioral deficits at seven years of age (40). Currently, recommended rates of weight gain for VLBW infants are based on intrauterine rates of growth (15 g/kg/day, AAP) (41) or estimates of fetal growth (18 - 21 g/kg/day, Ziegler) (15). However, the appropriateness of these recommendations has been debated. Although achieving growth rates equal to fetal/intrauterine weight gains is a widely accepted goal for VLBW infants, it does not compensate for the nutritional deficits that accrue in the early weeks of life (32).

Several possible reasons that may explain growth failure in VLBW infants are listed and discussed below:

(1) Medical and nutritional practices limit nutritional intakes as a result of feeding intolerance, medical complications and fear of necrotizing enterocolitis.

(2) Prescribed/Intended (PI) nutrition (energy and protein) is inadequate to sustain optimal growth and/or the prescribed intakes are not achieved in practice.

(3) Data related to Actual/Delivered (A/D) nutrition (energy and protein) intakes at the point of care are not available to make informed nutrition decisions.

(4) Trend data related to nutrition and growth (e.g., growth velocity, day of life infant returns to birth weight and DOL to reach full EN) at the point of care are not available to make informed medical nutrition decisions.

Physicians prescribe energy and protein intakes for VLBW infants that they believe to be consistent with current recommendations. However, the nutrition **delivered** is not always the same as what is **prescribed** as a result of many factors, some of which include medical complications (immature organs, inability to absorb nutrition and respiratory issues) and the inflexibility of established feeding protocols. Another early nutrition and feeding goal for VLBW infants is transitioning from PN, given shortly after birth, to EN. When VLBW infants reach full EN, they are considered 'stable' with their feeding regimen and thereafter are more likely to grow proportionately and meet published guidelines for growth velocity. VLBW infants who reach full EN sooner have a shorter length of hospital stay (42); however, the relationship of early nutrition to the VLBW infant's ability to reach full EN is unknown.

A gap in our knowledge exists regarding whether or not the P/I and A/D early nutrition (energy and protein intakes) meets Ziegler's theoretical estimated nutrient requirements for VLBW infants (22) and the relationship of the early nutrition to time to return to birth weight, time to reach full EN and growth outcomes at 36 weeks. These are the fundamental questions:

(1) Are prescribed energy and protein intakes consistently delivered in practice?

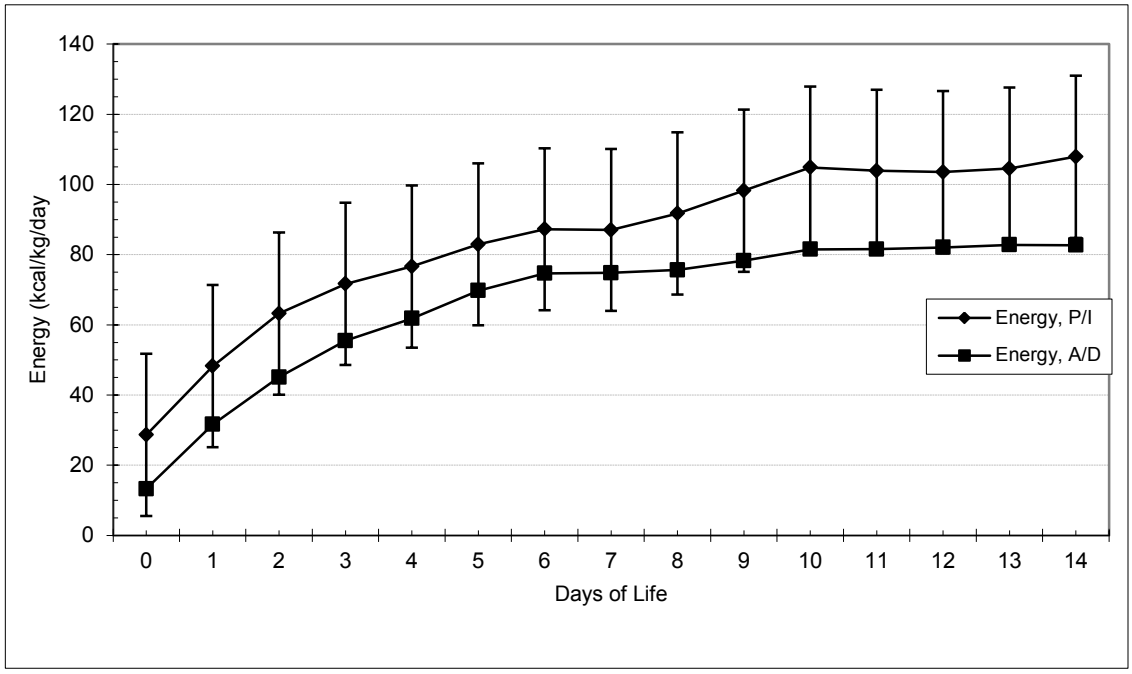
(2) Do the (P/I) or (A/D) energy and protein intakes of VLBW infants meet Ziegler's theoretical estimated nutrient requirements?

(3) Do theoretical estimated nutrient requirements support appropriate growth?

Data related to A/D nutrition (energy and protein) intakes as well as trend data related to nutrition and growth are needed at the point of care to make informed medical nutritional decisions. These data will allow optimization of feeding regimens to achieve positive growth and developmental outcomes in VLBW infants.

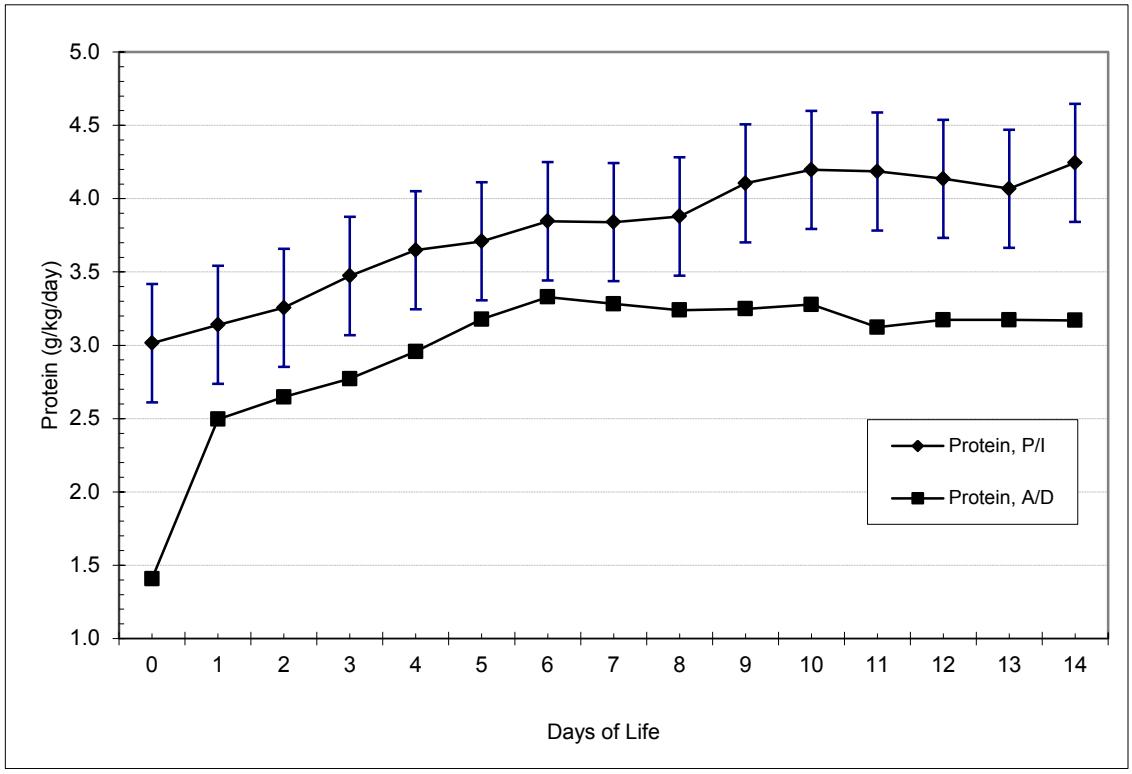
From preliminary data collected at Riley Hospital for Children at IU Health NICU, current practices were identified and factors that may influence early growth outcomes were assessed. Although these preliminary data were obtained in only one institution with a relatively small number of infants (n = 34), they revealed two significant observations in energy and protein intakes. The actual energy intake received was significantly lower than the prescribed energy intake, 66 ±13 kcal/kg/day to 84 ±16 kcal/kg/day, respectively with $p < 0.001$ level of confidence. The actual protein intake received was significantly lower than the prescribed protein intake, 3.0 ±0.4 g/kg/day to 3.8 ±0.4 g/kg/day, respectively with $p < 0.001$ level of confidence. Figures 1 and 2 shows the differences between prescribed and actual energy and protein intakes during the first 15 days of life in the VLBW infants studied. These VLBW infants have significant difficulty in tolerating the prescribed intakes, intravenous and/or enteral, of energy and/or protein during the first weeks of life.

Figure 1. Energy intake results from a preliminary study of VLBW infants (n = 34) during the first 15 days of life



Mean ±*SD* P/I days 1 - 15: 84 kcal/kg/day
Mean ±*SD* A/D days 1 - 15: 66 kcal/kg/day, $p < 0.001$

Figure 2. Protein intake results from a preliminary study of VLBW infants (n = 34) during the first 15 days of life



Mean ±*SD* P/I days 1 - 15: 3.8 g/kg/day
Mean ±*SD* A/D days 1 - 15: 3.0 g/kg/day, $p < 0.001$

VLBW infants are at high risk for long-term consequences, especially if nutrient goals are not achieved. Stephens and associates recently reported that during the first week of an ELBW infant's life, every 10 kcal/kg/day increase in energy and every 1 g/kg/day increase in protein were associated with a 4.6 point and 8.2 point increase, respectively, in the Mental Development Index at 18 months corrected age (14). This study emphasizes the importance of early nutrition, specifically energy and protein intakes during this critical period of brain growth. Table 1 presents the average energy and protein intakes during the first 7 days and weekly averages through week 4 for 148 ELBW infants. In the Stephens et al. study, the published guidelines for energy and protein were not reached until approximately the third week of life (14).

Table 1. Protein and energy intakes of ELBW infants (n = 148)

Day	Energy kcal/kg/day Mean ±*SD* (range)	Protein g/kg/day Mean ±*SD* (range)
1	31 ±12 (10 - 87)	0.4 ±0.5 (0.0 - 1.7)
2	45 ±12 (18 - 76)	1.0 ±0.5 (0.0 - 2.3)
3	53 ±11 (29 - 107)	1.5 ±0.5 (0.4 - 2.7)
4	62 ±12 (38 - 106)	2.0 ±0.5 (0.5 - 3.2)
5	71 ±14 (33 - 118)	2.4 ±0.6 (0.4 - 4.0)
6	76 ±14 (44 - 109)	2.0 ±0.7 (0.4 - 4.5)
7	81 ±14 (46 - 113)	2.9 ±0.7 (1.0 - 4.5)
Week 1	60 ±8 (40 - 91)	1.8 ±0.4 (0.5 - 2.8)
Week 2	94 ±13 (58 - 125)	3.3 ±0.4 (2.3 - 4.3)
Week 3	105 ±12 (83 - 138)	3.5 ±0.4 (2.4 - 4.5)
Week 4	105 ±14 (83 - 138)	3.5 ±0.5 (1.8 - 4.3)

Adapted from Stephens et al. (14)

3. Purpose and significance of the study

The overall purpose of the study was to assess current medical nutritional practices in three tertiary care newborn intensive care units during the first two weeks of

life and determine whether barriers and/or inconsistencies in P/I and/or A/D intakes resulted in a deviation from Ziegler's theoretical estimated nutrient requirements, and led to growth failure at 36 weeks' PMA. This study was a follow-up to the preliminary data that revealed a 20% lower A/D compared to the P/I nutritional intakes. A long-term goal is to determine the energy and protein intakes that will achieve short-term optimal nutrition status and will prevent negative long-term growth outcomes (including lung, brain, neurodevelopment).

The primary aim of the study was to assess nutrition (P/I and A/D energy and protein) relative to Ziegler's theoretical estimated nutrient requirements during the first two weeks of life for VLBW infants. Secondary aims were to correlate nutritional intakes to the infants' ability to reach full EN (defined as 100 ±10 kcal/kg/day) and evaluate the trends in nutritional and growth data (A/D energy and protein intakes relative to growth velocity).

This study provides a significant contribution to the science of nutrition and feeding of VLBW infants because of the meticulousness of the daily data collection and accurate calculations of P/I and A/D energy and protein intakes from multiple nutritional solutions with varied nutrient composition. The complexity of multiple feeding solutions and volumes that change and may be interrupted throughout the day in the VLBW infants is mind boggling. Some of the solutions include PN, IV fluids (both dextrose and other IV fluids such as blood, normal saline, etc.), mother's own milk and/or donor human milk (with different compositions) and various formula concentrations made with standardized formula recipes. Furthermore, the meticulous daily tracking and trending of the entire daily volume of fluids identified other issues that can markedly affect decisions made related to the medical-nutritional care. For example, the weights that were used by the clinicians in reporting volume of fluids per kilogram (kg) were sometimes inconsistent with the electronic nursing charting system and thus bedside decisions were

based on incorrect data. Finally, this study accurately determined the P/I and A/D energy and protein intakes from individually created recipes that met specific nutritional needs of approximately 25% of the infants in the study. The electronic tracking and nutritional data analysis system dramatically expanded the capabilities for query used in the study (43). A flow chart of inputs and outputs of the computerized system is given in Appendix A.

These data will prove to be valuable to the health care team as they seek to optimize nutrition to achieve desired growth and implement "best practice" feedings (15 and 17 - 21). Optimal nutrition is critical not only for early stages of development, including neurodevelopment of the VLBW infant but also for improved longer term outcomes (15). Furthermore, early nutrition mediates the severity of illness in ELBW infants (44). Longer term outcomes related to neurodevelopment and fetal programming are currently being explored (45). Fetal programming of metabolic pathways may lead to adverse health effects for these infants later in life (i.e., cardiovascular disease, obesity and insulin resistance) (45 and 46). Therefore, careful evaluation and implementation of early nutrition are paramount for the long-term health and well being of VLBW infants. Finally, the health care costs involved in caring for these high-risk infants have important public health implications. A shorter hospital stay (from improved growth rates) in the NICU of just one day for ~ 50 VLBW infants would save $330,000 - $550,000.

4. Hypotheses

Central Hypothesis. The provision of adequate nutrition (energy and protein that meet Ziegler's theoretical estimated nutrient requirements) (18 and 22) for VLBW infants during the first two weeks of life promotes earlier achievement of full EN defined as 100 ±10 kcal/kg/day and improved growth outcomes at 36 weeks post menstrual age (PMA).

The following specific aims and hypotheses evaluated the central hypothesis of the observational study:

Primary Aim. Assess nutrition (P/I and A/D energy and protein) relative to published guidelines during the first two weeks of life for VLBW infants in a tertiary care NICU.

Hypothesis 1: The percentage of the prescribed/intended energy (kcal/kg/day) intakes is significantly less than the recommended published guidelines (100% Ziegler's theoretical estimated energy requirements) for VLBW infants during the first week, second week and average of the first two weeks after birth.

Hypothesis 2: The percentage of the prescribed/intended protein (g/kg/day) intakes is significantly less than the recommended published guidelines (100% of Ziegler's theoretical estimated protein requirements) for VLBW infants during the first week, second week and average of the first two weeks after birth.

Hypothesis 3: The percentage of the actual/delivered energy (kcal/kg/day) intakes is significantly less than the recommended published guidelines (100% of Ziegler's theoretical estimated energy requirements) for VLBW infants during the first week, second week and average of the first two weeks after birth.

Hypothesis 4: The percentage of the actual/delivered protein (g/kg/day) intakes is significantly less than the recommended published guidelines (100% Ziegler's theoretical estimated protein requirements) for VLBW infants during the first week, second week and average of the first two weeks after birth.

Secondary Aim 1. Correlate actual delivery of energy (kcal/kg/day) and protein (g/kg/day) intakes during the first week of life with DOL to reach 100 kcal/kg/day EN.

Hypothesis 1: The A/D energy (kcal/kg/day) intake for week 1 is not significantly correlated to DOL to reach 100 kcal/kg/day EN of VLBW infants.

Hypothesis 2: The A/D protein (g/kg/day) intake for week 1 is not significantly correlated to DOL to reach 100 kcal/kg/day EN of VLBW infants.

Secondary Aim 2. Evaluate the trends in nutritional data; i.e., determine correlation of A/D energy and protein intakes in the first weeks of life to DOL return to birth weight, compare growth velocity (from DOL on which 100 kcal/kg/day EN were achieved to 36 weeks' PMA) to Ziegler's theoretical estimated fetal growth velocity and describe growth outcomes at 36 weeks' PMA.

Hypothesis 1: The A/D energy (kcal/kg/day) for week 1 is not significantly correlated to DOL return to birth weight.

Hypothesis 2: The A/D protein intake (g/kg/day) for week 1 is not significantly correlated to DOL return to birth weight.

Hypothesis 3: The growth velocity from DOL on which 100 kcal/kg/day EN were achieved to 36 weeks' PMA is not significantly different from Ziegler's theoretical estimates for fetal growth velocity (18 and 19).

5. Scope of the Study/Limitations of the Study

The scope of the study includes early nutrition for critically ill VLBW infants in a tertiary care NICU and the relationship to Ziegler's theoretical estimated energy and protein requirements and growth milestones. Additionally, growth velocity from DOL on which 100 kcal/kg/day EN were achieved to 36 weeks' PMA was compared to Ziegler's theoretical estimated fetal growth velocity and growth outcomes at 36 weeks' PMA were determined. The number of infants < 30 weeks gestational age at birth in different weight categories (500 - 700, 701 - 900, 901 - 1200, and 1201 - 1500 g) and appropriate for gestational age (AGA) and small for gestational age (SGA) categories was inadequate to determine whether there were differences within the subgroups. Although three different

tertiary care nurseries with different populations provided VLBW infants for the study, the study still needs to be extended to other NICUs within the state and country.

Additionally, the scope of the study included the development of a computerized tool that stored the collected data, calculated the protein and energy of each volume of solution both from the P/I and A/D from each nursery, de-identified the personal identifiers and stored the data on a flash drive. These data were transferred to an Excel spreadsheet that could be sent electronically to the investigator.

6. Methodology

An observational study of the feeding, nutrition and early growth of VLBW infants in three tertiary care NICUs compared early nutrition (P/I and A/D energy and protein intakes) to Ziegler's theoretical estimated nutrient requirements during the first two weeks of life and correlated early nutrition to time to return to birth weight, time to reach full EN and growth outcomes at 36 weeks' PMA.

The newly developed computerized tool utilizes a query approach to facilitate data entry and analysis in a more efficient and effective manner. Its unique features provide greater accuracy for the energy and protein calculations, particularly in situations with complicated feeding recipes. The standard recipes were entered into the computer system prior to the study, but there are specific times when an infant requires a unique recipe. The energy and protein content of each new recipe was entered into the system and given a distinctive name for future utilization with other patients.

7. Summary

Optimal nutrition during the first two weeks of life for a premature infant is imperative for short-term and long-term health benefits. Data from the multi-sites study elucidated nutritional practices for the first two weeks of life for the VLBW infant and described infant's energy and protein intakes and associated growth outcomes. It was hypothesized that the percentage of the P/I and the A/D energy and protein intakes were

significantly less than the desired recommended theoretical estimated nutrient requirements (100% of Ziegler's estimated nutrient requirements (18)) for VLBW infants during the first two weeks after birth. A secondary aim of the study was to explore the effect of early nutrition (energy and protein) on the VLBW infant's ability to return to birth weight, to achieve 100 kcal/kg/day of EN and to observe growth velocity trends.

8. Definition of terms

Actual/delivered Nutrition (A/D): Nutrition that is actually delivered to a VLBW infant is recorded in the infant's medical chart under the input and output section (I and Os). The volume (mL/kg/day) amount provides the energy (kcal/kg/day) and protein (g/kg/day) from calculations based on the known compositions of PN and EN.

Chronological Age (also stated as postnatal age): Time elapsed after birth (47).

Corrected Age (also stated as adjusted age): Term most appropriately used to describe children up to 3 years of age who were born preterm (51). Corrected age is calculated by subtracting the number of weeks born before 40 weeks of gestation from the chronological age (47).

Day of Life (DOL): Days of life after birth (47).

Enteral Nutrition (EN): A route to provide feedings through a tube placed thru the nose or mouth into the stomach or the small intestine. A tube in the nose is called a nasogastric tube, nasoenteral tube, or orogastric tube (48).

Extrauterine Growth Restriction (EUGR): A situation that occurs when an infant's weight is average for its gestational age at time of birth but its weight has fallen to less than or equal to the 10^{th} percentile for its corrected gestational age at time of hospital discharge (29).

Extremely Low Birth Weight (ELBW): Infants weighing between 501 and 1000 g (about 18 to 35 ounces) at birth (49).

Gestational Age (GA): Time elapsed between the first day of the last normal menstrual period and the day of delivery (47).

Parenteral Nutrition (PN): Intravenous feeding that provides infants with fluid and essential nutrients when they are unable to feed by mouth or use their GI tract (54).

Prescribed/intended Nutrition (P/I): Nutrition prescribed by a neonatologist and/or medical provider and recorded in the medical chart under physician orders. Nutrition is prescribed in a volume amount (mL/kg/day) of PN and/or EN. Energy (kcal/kg/day) and protein (g/kg/day) were calculated from the volumes and known compositions of PN and EN (50).

Postmenstrual Age (PMA): Time elapsed between the first day of the last menstrual period and birth (gestational age) plus the time elapsed after birth (chronological age) (47).

Very Low Birth Weight (VLBW): Infants weighing less than 1500 g at birth (49).

CHAPTER 2: REVIEW OF THE LITERATURE

1. Overview

The American Academy of Pediatrics (AAP) has recognized the importance of optimal nutrition for very premature infants yet no set guidelines have been established for the key nutrients during the first two weeks of life or in the transitional phase from PN to EN (51). The AAP Consensus has provided PN and EN recommendations for premature infants to mimic the rate of weight gain and body composition of a normal fetus of the same postconceptional age (51). However, the reality of the initial disruption of delivery of nutrients through the premature birth process is challenging and unique to each infant. Therefore, it has been difficult to standardize and implement effective feeding protocols because of medical complications and uncertainty of outcome for any specific situation. Additional ambiguity occurs concerning effective implementation practices, especially when medical complications transpire.

Ziegler's theoretical estimates used as recommendations for nutritional support for premature infants have become recognized as one of the established standards in providing estimates for nutrition and expected growth outcomes for the premature infant (22). They address the significance of early nutrition and its impact on improved growth and neurodevelopmental outcomes. He describes two separate and different approaches when determining the nutrient requirements of premature infants: the "Factorial Approach" and the "Empirical Approach" (15 and 22). He developed the "Factorial Approach" not only as an estimate of necessary nutrient requirements, but also as a corresponding estimate of expected growth velocity by weight categories for premature infants. This observational study will refer to these recommendations as the Ziegler's theoretical framework of nutrient requirements.

The least desirable growth outcome is the premature infant's failure to grow, which is commonly referred to as "growth failure", "postnatal growth restriction" and "extrauterine growth restriction (EUGR)." This observational study will use the EUGR terminology and discuss the daily energy and protein intakes of VLBW premature infants when compared against the theoretical estimated nutrient requirements (Ziegler's guidelines) and the actual growth outcomes at predetermined milestones as defined by the Ziegler's theoretical estimated fetal growth velocity. In addition to Ziegler's guidelines, other literature related to current nutritional practices and their impact on growth outcomes will be reviewed.

2. Ziegler's Theoretical Framework

Introduction to Ziegler's Theoretical Framework. Not only has EUGR of preterm infants become a universal financial burden, as noted in Chapter 1, but it also has a major impact on society and families. When EUGR occurs, the maturation of the preterm infant's vital organs is delayed, which magnifies the negative effects of other complications such as chronic lung disease, visual and hearing loss and neurodevelopmental delay. Attempts to "catch-up" and overcome growth deficits result in an unnecessary accelerated rate of weight gain which may create other long-term consequences, such as insulin resistance, obesity and possibly altering epi-genetics for subsequent generations.

Research has demonstrated that early nutrition can alter these negative long-term outcomes in VLBW infants. Still, standardized feeding protocols remain undeveloped for VLBW preterm infant during the first two weeks of life. As clinicians focus their efforts towards keeping the preterm infant alive, there is relatively little emphasis on the amounts of energy or protein delivered to these infants. Often, the process of calculating energy and protein is time-consuming, rendering nutritional data incomplete or delayed at best. Previously completed research typically recorded

nutritional data at intermittent intervals instead of daily, making it difficult to establish a true relationship between nutritional intakes, specific feeding regimens and growth outcomes.

Although difficult to achieve, evidence is emerging that early nutrition support improves growth and neurodevelopmental outcomes. Most practitioners report the prescribed feeding regimen at the point-of-care with the assumption that the actual/delivered is the same as the prescribed/intended, especially during the first two weeks of the preterm infant's life. This view may misrepresent the actual delivered energy and protein.

One of the most important advances in the field of nutrition for the premature infant was the establishment of theoretical estimated nutrient and theoretical estimated fetal weight gain requirements. In Ziegler's published guidelines, these estimates are set by the premature infant's body weight at birth. Ziegler places each infant into one of the following weight categories (500 - 700, 701 - 900 and 901 - 1200 grams) as shown in (Table 2, (21)). Ziegler's theoretical estimated nutrient requirements are the theoretical framework used to support premature infants who receive medical/nutritional care in newborn intensive care units.

The theoretical estimates for energy and protein requirements were based upon fetal data (15, 52, and 53). Unfortunately, in clinical nutritional support of VLBW infants, it is not clearly known how well these estimates are being met during the first weeks of life and whether these estimates prevent EUGR at 36 weeks' PMA. In general, immaturity, especially in VLBW infants, medical complications and medical nutritional practices hinder the provision of early nutrition.

Within the last decade, Ziegler made a significant case for providing what he called "early aggressive nutritional support". Ziegler (15, 22, and 27) considers aggressive nutrition to be the "best nutrition" that can be provided, considering the

current state of knowledge and technology. Specifically, Ziegler defines early aggressive nutritional support as the administration of PN containing amino acids shortly after birth and then increasing the concentration of amino acids to 3.0 - 4.0 g/kg/day during the first week after birth. The primary goal of early aggressive nutrition is to provide positive nitrogen balance and to prevent protein energy malnutrition (15 and 52 - 54). In other words, the objective of early aggressive nutrition support is to support the growth and composition of growth similar to a fetus in utero of the same age. The American Academy of Pediatrics, Committee on Nutrition (51), recommends that the levels of nutrients provided be sufficient (a) to maintain postnatal rate of growth and composition of weight gain as a similar fetus in utero of the same gestational age and (b) to maintain normal concentrations of nutrients in blood and tissue.

Table 2. Ziegler's theoretical estimated protein and energy requirements determined by the factorial approach

	Body Weight, g					
		701 - 900	**901 - 1200**	**1201 - 1500**	**1501 - 1800**	**1801 - 2200**
Fetal Weight Gain						
g/day	13	16	20	24	26	29
g/kg/day	21	20	19	18	16	14
Protein, g						
Inevitable loss	1.0	1.0	1.0	1.0	1.0	1.0
Growth (accretion)	2.5	2.5	2.5	2.4	2.2	2.0
Required Protein Intake						
Parenteral	3.5	3.5	3.5	3.4	3.2	3.0
Enteral	4.0	4.0	4.0	3.9	3.6	3.4
Energy, kcal						
Loss	60	60	65	70	70	70
Resting expenditure	45	45	50	50	50	50
Miscellaneous expenditure	15	15	15	20	20	20
Growth (accretion)	29	32	36	38	39	41
Required Energy Intake						
Parenteral	89	92	101	108	109	111
Enteral	105	108	119	127	128	131
Protein/energy, g/100 kcal						
Parenteral	3.9	4.1	3.5	3.1	2.9	2.7
Enteral	3.8	3.7	3.4	3.1	2.8	2.6

[1]Shown intakes are needed to achieve fetal weight gain. Nutrient needs are stated relative to body weight and apply regardless of postnatal age. All values are per kg/day except where noted.

Weakness of Ziegler's Theoretical Framework. A weakness in Ziegler's theory becomes noticeable with the difficulty of providing the higher amino acid intakes to the VLBW infant within hours after birth. This occurs for several reasons:

(1) Preterm infants are physiologically immature and medically unstable.

(2) Nutritional care protocols and monitoring systems are not available to support these higher levels of amino acid intakes.

(3) Neonatologists are reluctant to administer these levels of amino acids greater than 3.0 g/kg in PN because they have not been studied and documented as safe (24).

During the first hours after birth, neonatologists are concerned primarily about the preterm infant's uncertain and perilous medical condition. Respiratory failure (inability to breathe), temperature instability (hypothermia), infection and medical stability (keeping the infant alive) are typically their primary concerns. Nutrition, although important, is not the highest priority while the health care team is medically stabilizing the critically ill infant. Despite being prioritized lower than cardiopulmonary care, PN during the first day after birth has become routine in many NICU's.

In general, few nutritional care protocols are available in NICUs and growth outcome studies are even less available. Thus, a wide range of nutrition practices exists in NICUs throughout the United States with little evidence to choose the most effective protocol for a specific situation. Therefore, "evidence based" data that support the long-term efficacy and safety of Ziegler's theory are very difficult to obtain or not been performed.

Finally and most important, neonatologists honor the creed, "First, do no harm." Neonatologists cite concerns regarding neurotoxicity from higher amino acids given during the first hours after birth and the risks of feeding intolerance and necrotizing enterocolitis, both associated with EN intake in preterm infants. Ziegler responds by

asking, “Where is the evidence that our current practice does no harm?” In fact, ample evidence exists that the nutritional needs of the premature infant are not currently being met and many become malnourished during their hospital stay (1, 3, 5, 16, 29 - 30, and 39). Another weakness in the application of Ziegler’s theory is that long-term clinical trials of growth and neurological outcomes as well as potential adverse consequences in adulthood have not been performed.

Gap in Ziegler’s Theoretical Framework. It is important that neonatal clinicians recognize the barriers and obstacles to the application of Ziegler’s theory. One of the gaps in applying Ziegler’s theory is the limited availability of accurate protein and nutrient intake data of VLBW infants, especially on a daily basis. Collecting data on actual intakes and growth outcomes is a very tedious and labor-intensive task. Therefore, it is often neglected and/or performed sporadically and/or evaluated too late to be of practical use. In place of actual intakes, the health care team may use physician orders to estimate, or forecast, fluid volumes, energy and key nutrient intakes. In practice, the actual energy and protein intakes are often 15 - 20% lower than the amounts ordered during the first weeks after birth. Thus, the resulting rates of growth outcomes are not related to the P/I but to the A/D energy and protein intakes. Many NICUs do not have an expert neonatal-pediatric dietitian (registered dietitian) who is trained to develop nutrition protocols that apply Ziegler’s theory of early aggressive nutrition support, to accurately monitor and evaluate the actual nutrient intakes compared to growth and to analyze the effectiveness of the nutrition protocol. The NICU at Sanford Children’s Hospital South Dakota was able to greatly improve the nutrition growth outcomes of its premature infants by adding a registered neonatal-pediatric dietitian (55).

Ziegler’s Theoretical Framework and Kuhn’s Characteristics of a Good Theory. According to Kuhn (56), the characteristics of a good theory are accuracy, consistency, scope, simplicity and fruitfulness. Kuhn’s characteristics of a good theory

are summarized and Ziegler's guidelines evaluated in each of the five characteristics of a good theory in Table 3.

In summary, based upon Kuhn's characteristics of a good theory, the theoretical framework is **accurate**, at least for short-term outcomes but further studies are needed to confirm long-term outcomes. The **scope** is somewhat limited, i.e., encompasses short-term rates of weight gain and body composition of the gain but not longer term growth and neurological outcomes. Ziegler's theoretical framework, when applied to real world clinical cases, has been extremely **fruitful** in stimulating further research and discussion. The theoretical framework is **consistent** with AAP recommendations of mimicking fetal growth and it has **simplicity** as there is no other theory at this time.

Table 3. Kuhn's characteristics of a good theory applied to Ziegler's theoretical estimated nutrient requirements

Kuhn's Characteristics of a Good Theory	Definition of Kuhn's Characteristics of a Good Theory	Application to Ziegler's Theoretical Estimated Nutrient Requirements
• Accuracy	• Demonstrates predictive accuracy (considered trustworthy in conventional scientific terms)	• Accurately predicts the short term benefits of higher amino acid solutions • Supports a positive nitrogen balance and protein synthesis • Emerging evidence in improvements in neurological outcomes
• Consistency	• How well all the components of a theory fit together • How consistent the theory is with available scientific knowledge	• Derived from the composition of fetuses • Fetal data for energy, protein and minerals at various gestational ages are known • Fetal data were summarized and estimation were determined to support the body composition ○ Known absorption and bioavailability for the various nutrients were utilized in the estimations • Consistent with accepted normative nitrogen balance (protein synthesis) and growth standards for infants in utero
• Scope	• How much a theory attempts to explain	• Theoretical estimated nutrient requirements are widely used as published guidelines for the provision of nutrition • Derived from fetal composition data which provide estimates of the nutrients required to support rates of growth and composition of weight gain that match in utero gains
• Simplicity	• Notion that, all other things being equal, the simpler of two theories is preferred	• No other theories based on empirical data • Elegantly simple "suboptimal nutrition equals growth failure" • Growth failure is a marker for poor neurocognitive outcomes
• Fruitfulness	• Notion that a theory may be important, not simply by its apparent truthfulness, but also by stimulating further research	• Fetal growth is considered the norm • It is stimulating the most exciting and relevant research

Conclusions and Clinical Application of Ziegler's Theoretical Framework.

Ziegler's theoretical framework of early aggressive nutrition support for premature infants is the only sound (good) theory available for determining protein and nutrient recommendations for premature infants. In fact, short-term studies have confirmed its safety and efficacy in improving nitrogen (protein) balance without adverse consequences such as metabolic acidosis, protein toxicity or intolerance and blood amino acid imbalances. Emerging evidence suggests that 3 to 4 g amino acids/kg/day, the amount recommended by Ziegler, improves growth, lean body mass and neurocognitive development, however, further studies are needed (2 and 57 - 62). Finally, expert neonatal-pediatric dietitians are a vital member of the health care team in the NICU. They are the individuals advocating the application of Ziegler's recommendations for accurately estimating energy and protein intakes and promoting optimal growth, lean body mass and neurological development.

3. Historical Background

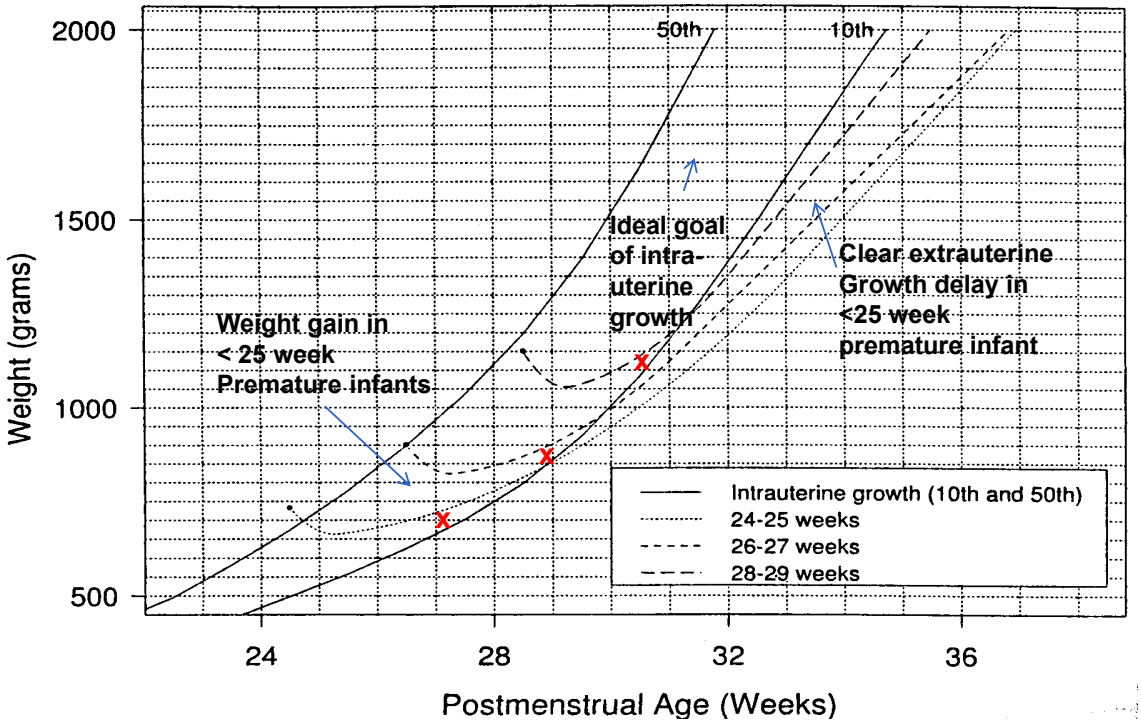
Over the past 35 years, the medical care, nutrition and feeding of premature infants have improved with each advancement in major medical and nutritional practices. In the 1970's, ELBW infants (< 1000 g birth weight) had high rates of mortality (> 50 %) and morbidity, including cognitive disabilities and learning problems, chronic lung disease, cerebral palsy, vision and hearing problems. During this era, early aggressive nutrition support was considered potentially life threatening to the baby because of concern for neurotoxicity from amino acid solutions that were not designed to support preterm infant growth and development. PN was started late (as long as 10 to 14 days following birth) with low doses of amino acids (AA) 0.5 - 1.0 g/kg/day and no lipids. Enteral feedings often were withheld for long periods because of concern for necrotizing enterocolitis (life threatening gastrointestinal inflammation and ischemia) and formulas designed for premature infants had not yet become commercially available.

Suboptimal nutrition support, i.e., inadequate EN and PN in premature babies, frequently resulted in a significant deficit in the amount of protein and energy given compared with the amount the infant would have received in utero. This is at least partially responsible for the growth delay in the first weeks after birth in these infants. In the early 1980s, formulas became available for premature infants with increased concentrations of energy, protein and other nutrients to better support growth and improve composition of accumulated tissue. By the early 1990s, new amino acid solutions for PN became available that supported growth and normal blood concentrations of amino acids in VLBW infants (15, 18, 19, and 21). Ziegler, one of the researchers who designed the amino acid solutions for premature infants, proposed the theory of 'early aggressive nutritional supplementation' to support intrauterine growth composition and rates of gain in weight, length and head size. Although this was more than a decade ago, evidence is emerging that postnatal growth delay (extrauterine growth restriction) is a concern not only because of growth failure but also because of the association with irreversible long-term neurodevelopmental delays and learning disabilities (2 and 31).

Growth failure (Figure 3, (31)), referred to as EUGR, in premature infants resulted from an inability to provide adequate early nutrition that now is linked to improved respiratory function and neurodevelopmental outcomes (2, 3, 25, and 54). An important advance in the field of nutrition for the premature infant was the estimation of nutrient requirements and growth determined by the factorial method from fetal data referred to in this paper as Ziegler's theoretical estimated nutrient requirements (15, 22, and 52 - 53). Ziegler's estimated nutrient requirements and Ziegler's theoretical estimated fetal growth velocity is the theoretical framework used to support premature infants in the real world of medical/nutritional care in NICUs.

The following reviews extrauterine postnatal growth restriction (EUGR) and the evidence of its association with poor neurocognitive development and respiratory function, the limited studies that document lower nutrient intakes during the first two weeks of life and, if available, the relationship of early nutrition to growth indicators (2, 3, 14, 23, 25, 27 - 28, and 57). The nutrient requirements will be reviewed more extensively, especially the theoretical estimated nutrient requirements published and widely used as a standard guideline for VLBW infants. A thorough understanding of the nutrient requirements and their derivation is a prerequisite for designing effective interventions for improving early nutrition. Ziegler's theoretical estimated nutrient requirements were used as the theoretical framework for this study, i.e., determining the relationship of prescribed/intended and actual/delivered early nutrition to the theoretical estimates and indicators of growth in three tertiary care NICUs. The primary question is "With current medical nutritional practices in tertiary care NICUs, are the energy and protein intakes and indicators of nutrition/growth meeting Ziegler's theoretical estimated nutrient requirements and Ziegler's theoretical estimated fetal growth velocity to match in utero fetal growth? If not, why not?"

Figure 3. Extrauterine growth restriction in VLBW infants

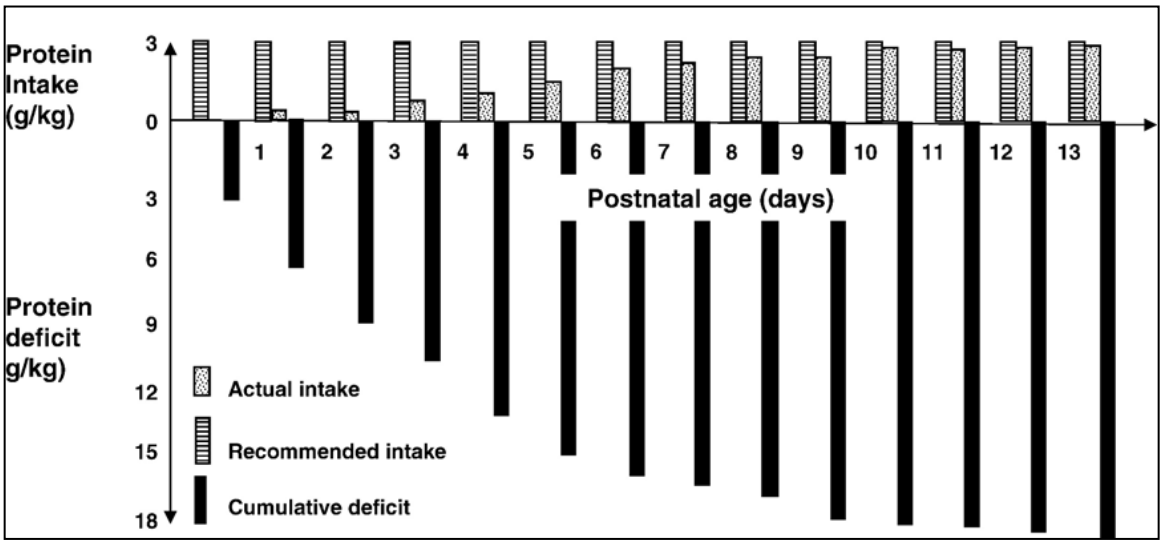


Postnatal growth restriction. The medical clinician attempting to replicate fetal life approximating normal growth in utero has a challenging task at hand. It is complicated to deliver protein and energy requirements that support growth without higher fat mass, nutrient deficits and long-term metabolic consequences when feeding the VLBW infant. EUGR is a universal condition for VLBW infants and is the second most contemplated concern in the NICU only surpassed by respiratory (breathing) issues.

Cause of growth restriction. The cause of growth restriction has been thought to be due to inadequate nutrition (4 and 22). A number of observational studies documented slow weight gain and low protein intakes in premature infants (2, 4, 5, 14, and 58). The evidence is compelling that current nutritional practices may still fall short in providing sufficient dietary protein for premature infants, especially in VLBW infants. The inability to know actual/delivered amounts of energy and protein results in inconsistent nutritional delivery and illustrates the incredible challenge that clinicians face in making nutritional recommendations on a daily basis. Another serious concern is the inability to know the energy and protein amounts of the combined nutritional regimens for the VLBW infants.

Typically, VLBW infants receive immediate provision of energy as intravenous dextrose solutions, followed by increasing amounts of parenteral amino acids. The gradual increase in delivery of protein and energy during the first days of life inevitably result in a significant nutrient deficit. Embelton et al. calculated the cumulative protein deficit in infants less than 31 weeks GA at birth for postnatal days of life 0 through 13 (4) (Figure 4, (54)). The cumulative protein deficit by the end of the second postnatal week was estimated to be approximately 18 g/kg/day, assuming a protein requirement of 3 g/kg/day and the energy deficit was < 600 kcal/kg/day, assuming a requirement of 120 kcal/kg/day.

Figure 4. Cumulative protein deficit in infants < 31 weeks for postnatal days 0 - 13



Consequences of growth restriction. Within the last decade, a number of studies have established beyond any doubt that EUGR is associated with impaired neurocognitive development (3, 4, 7, and 32). This is not surprising because when growth occurs, all the organs of the premature infant grow and develop including the lungs and brain. The reasons for low nutrient intakes in VLBW infants are not easily determined. Almost certainly one of the reasons that nutrients, either enterally or parenterally, were provided cautiously during the first days of life was because it was assumed that they were potentially hazardous and that growth restriction was harmless. In 2009, Stephens et al. published a study (14) that documented the deleterious effects of low energy and protein intakes (near starvation) on neurocognitive development at 18 months of age. Since this report, anecdotal reports suggest that there is a greater awareness of postnatal growth restriction and this increased awareness is leading to different ways of approaching this complex medical issue. The association between growth failure and late cognitive development does not necessarily mean that growth failure per se is the cause of impaired neurodevelopment. It is more likely that they share a common cause, inadequate nutrition (15). The only study that directly links neurodevelopment to nutrient intakes rather than growth failure is that of Stephens and associates (14). Furthermore, early aggressive nutrition mediates the influence of severity of illness in ELBW infants and improves recovery from respiratory distress and chronic lung disease (44).

4. Review of Similar Studies

Berseth (42) in 1992 studied the response of the preterm infant's intestine to enteral feedings at different postnatal ages. She studied two groups consisting of 27 preterm infants at 28 to 32 weeks of gestational age. Preterm infants were randomly assigned to receive hypocaloric EN on postnatal days 3 to 5 (early feeding) or on days 10 to 14 (late feedings). There were three study times of recorded results of manometry

of the gastroduodenum and determined fasting plasma concentrations of gastrin, gastric inhibitory peptide, neurotensin and peptide YY. Observations from the study concluded that **early-fed infants** were able to tolerate full oral nutrition sooner, had **fewer days of feeding intolerance** and had **shorter hospital stays**. This study was the first to verify the importance of early trophic enteral feeds due to the association with earlier nutrition of preterm infants' intestinal function and resulted in improved feeding tolerance.

Olsen et al. (58), in 2002 in a retrospective study, reported energy (kcal/kg/day) and protein (g/kg/day) mean intakes on DOL 3, 7, 14 and 21 from six NICUs in New England from October 1994 to June 1996 for 564 infants. Weights were collected on DOL 0, 3, 7, 10, 14, 21 and 28. Her goal was to explain growth differences in extremely premature (< 30 weeks GA) infants and to identify NICU practices and complications associated with growth (positive and negative) in this population. The average energy (protein) mean intakes for all six NICUs were: DOL 3 44 kcal/kg/day (0.6 g/kg/day); DOL 7 74 kcal/kg/day (2.1 g/kg/day); DOL 14 94 kcal/kg/day (2.5 g/kg/day); DOL 21 102 kcal/kg/day (2.5 g/kg/day). The conclusions of this study reported that variation in nutrition explained much of the difference in growth among the NICUs studied. Her results concluded the best indicator for growth was protein: the model predicted that adding **1 g/kg/day of protein** to the mean intake for their sample **increased growth by 4.1 g/kg/day**. The study also demonstrated the mean intake of calories and protein failed to meet recommended levels. However, the methods did not state if the nutritional intakes were taken from physicians prescribed nutrition or actual intakes recorded in the nursing input and output chart.

Poindexter et al. (25), in 2006 completed a secondary analysis of 1018 infants from data collected in a randomized, clinical trial of glutamine supplementation between October 1999 and August of 2001. She and her colleagues studied the effects of early provision of parenteral amino acids and its association with improved growth and

neurodevelopmental outcomes. The infants were assigned to two groups: early amino acids group (18% of infants) identified as > 3 g/kg/day of amino acids at ≤ 5 days of life and late amino acids (82% of infants) identified as < 3 g/kg/day of amino acids or > 5 days of life.

It was reported that energy intakes from PN and EN averaged over the first 5 days of life was 45.3 kcal/kg/day (Early group) and 32.9 kcal/kg/day (Late group); and the first 20 days of life was 81.4 kcal/kg/day (Early group) and 75.7 kcal/kg/day (Late group). The average mean gestational age was 26 weeks. The nutritional intake was recorded as actual/delivered energy (kcal/kg/day). The outcome of the study demonstrated that the early amino acids group was associated with **significantly better growth at 36 weeks' postmenstrual age** and fewer infants who received **early amino acids** were found to have **suboptimal head growth** at **18 months corrected age.**

Valentine et al. (59), in 2009 reported her study that compared 308 preterm infants in a prospective study (2005 and 2006) who received amino acids within the first 24 hours to 132 preterm infants in a retrospective study (2004) who did not receive amino acids within the first 24 hours. The hypothesis tested that early administration of amino acids (within the first few hours of life) to infants born at less than 1500 g would be associated with fewer infants that were less than the 10^{th} percentile at 36 weeks' PMA than infants that received amino acids after the first 24 hours. This resulted in three significant outcomes:

(1) Fewer infants fell below the 10^{th} percentile ($p < 0.001$) in the early amino acid group,

(2) Infants in the early amino acid group had significantly greater weight gains than did the late amino acids group ($p < 0.003$) and

(3) Shorter duration of PN was associated with early amino acids supplementation ($p < 0.001$).

Stephens et al. (14), in 2009 reported a study of 148 ELBW (≤ 1000 g) infants from data collected from January 1, 2000 to December 31, 2001. She collected daily protein and energy intakes by chart review for the first 4 weeks of life. In the follow-up phase, 124 infants who returned at 18 months corrected age were tested for Bayley Mental Development Index, Psychomotor Development Index and growth. The results of the study after adjusting for confounding variables found that week 1 energy and protein intakes were each independently associated with the Mental Development Index. They reported that every 10 kcal/kg/day was associated with a 4.6 point increase in the Mental Development Index and each g/kg/day in protein intake was associated with an 8.2 point increase in the Mental Development Index; higher protein intake was also associated with lower likelihood of length < 10^{th} percentile. The average energy and protein intakes for week 1 were 60 kcal/kg/day and 1.8 g/kg/day; week 2 was 94 kcal/kg/day and 3.3 g/kg/day.

Ehrenkranz et al. (44), in 2011 completed a secondary analysis of 1,366 infants whose data was collected from a randomized, clinical trial of glutamine supplementation between October 1999 and August 2001. He and his colleagues examined whether nutritional support provided to “more critically ill” infants differed from that provided to “less critically ill” infants during the initial weeks of life and if, after controlling for critical illness, that difference is associated with growth and rates of adverse outcomes. They reported that compared with more critically ill infants, less critically ill infants received significantly more total nutritional support during each of the first 3 weeks of life, had significantly faster growth velocities, less moderate/severe bronchopulmonary dysplasia, less late-onset sepsis, less death, shorter hospital stays and better neurodevelopmental outcomes at 18 - 22 months corrected age. He reported 52.0 kcal/kg/day for DOL 1 - 7 for infants on mechanical ventilation < 7days and 42.7 kcal/kg/day for DOL 1 - 7 for infants on mechanical ventilation > 7 days.

Ramel et al. (39), in 2012 assessed the duration and clinical determinants of poor linear growth and its relationship to neurodevelopment in preterm infants. A retrospective review was completed of 62 appropriate for gestational age VLBW preterm infants ≤ 30 weeks gestational age at birth (January 2003 and July 2007) and return for all 3 routine newborn follow-up appointments at 4, 12 and 24 months chronological age. She reported the results as mean length Z-score was lower than weight Z-score (p = 0.004) at hospital discharge, was related in part to illness severity and remained lower than baseline length Z-score until 24 months chronological age. She also described controlling for weight Z-scores and head circumference Z-scores at each age, lower length Z-scores at 4 and 12 months chronological age was associated with lower cognitive function scores at 24 months chronological age ($p \leq 0.03$). They concluded nutritional and non-nutritional factors influenced the degree of pre- and post-discharge linear growth suppression in VLBW infants, which in turn was negatively associated with developmental outcomes at 24 months chronological age. Furthermore, since linear growth correlates with brain growth and indices for a number of clinical factors, it is an important biomarker that can be used in VLBW infants to predict long-term developmental outcomes.

Bloom (27) in 2003 studied site-specific average weight gain during the first 28 days for VLBW infants. They developed a team of 6 neonatologists and 1 nurse that reviewed processes that might influence growth and developed a structured observation guide for site visits. The researchers divided the infants that were obtained from an existing administrative database for the period January 1, 1997 through June 30, 1999 by growth velocities. The team compared the practices of sites that had the highest growth velocities to sites that had the lowest growth velocities. The team recorded 16 meaningful differences between the high and low growth velocity sites. Meaningful differences were defined as processes observed in all of the high and none of the low

centers. The directors of each site received a list of the meaningful differences in August 2000 along with their site-specific weight-gain performance. The time period of post educational intervention period from January 1 through September 30, 2001 was compared to the database period. Reported results included average daily weight gain during the first 28 days which increased from 10.4 ±6 g for neonates cared for in 1999 to 12.5 ±6 g for neonates cared for in 2001. Thirty-nine of 51 units noted improvements, 4 were unchanged and 8 noted a decrease in average weight gain. Their conclusion was that identification of meaningful differences in clinical nutrition practices with subsequent changes to existing practices can rapidly improve clinical outcomes.

Hans (60) in 2009 surveyed NICU directors, neonatal fellowship directors, neonatologists, neonatal nurse practitioners and neonatal dietitians about feeding strategies for 3 preterm infant weight groups. The reported results from a 23% return of 176 survey responses indicated that the majority initiated PN for very preterm infants on the first day of life, 91% increased protein delivery daily and breast milk was prescribed most commonly for the first enteral feeding. Enteral feedings were started earlier and increased faster than in the past, especially for ELBW infants.

Martin et al. (61), in 2009 described nutritional practices in the first month of life for 1187 infants born at 23 to 27 weeks of gestation at 14 institutions between 2002 and 2004. A prospective cohort study design compared nutritional intakes during the first week and on days 14, 21 and 28 to recommended guidelines. Martin and colleagues reported from their cohort of infants the median protein intake provided by both parenteral and enteral routes was 1.0 g/kg/day on day 1 and 3.5 g/kg/day by day 4 with the median protein intake at 3.5 g/kg/day between days 3 and 28. The median for energy was on DOL (1) 26 kcal/kg/day; (3) 59 kcal/kg/day; (7) 79 kcal/kg/day; and (14) 92 kcal/kg/day. The median for protein was on DOL (1) 1.0 g/kg/day; (3) 3.0 g/kg/day; (7) 3.5 g/kg/day; and (14) 3.4 g/kg/day. The results reported that protein and fat delivery

approximated current nutritional recommendations, whereas carbohydrate and total energy intake delivery did not. Although, the EUGR weight for gestational age below the 10th percentile) was 75% of the infants at 28 days, compared with only 18% at birth, the growth velocity of their infants exceeded the current guideline of 15 g/kg/day. Martin reported early (day 7) nutritional practices were positively associated with growth velocity measured between days 7 and 28.

Hanson et al. (62), in 2011 reported a retrospective chart review of < 1500 g birth weight (n = 32) and after implementation of nutrition practice changes designed to decrease EUGR (n = 49). They listed the following changes implemented: early aggressive PN, early EN, trophic feedings, continuous feeding administration, protein fortification of 24 kcal/oz mother's own breast milk and development of a "feeding intolerance" algorithm. The investigators divided the cohort into subgroups ≤ 1000 g and 1000 - 1500 g and evaluated for demographics, growth parameters, and secondary feeding and discharge outcomes. Their results after implementation of the nutrition practice changes decreased EUGR, defined by weight ≤ 10th percentile at discharge, from 57% in the pre-implementation group to 28% in the post-implementation group (p = 0.01). They also reported a significant increase in weight-for-age percentile for the 1001 - 1500 g weight group from the 13th to the 27th percentile at 36 weeks' PMA (p = 0.004 and p = 0.01, respectively). Other benefits reported: chronic lung disease decreased and days of PN and central line use were decreased (p = 0.02 and p = 0.07, respectively) significantly. The authors reported significantly better growth outcomes without increasing undesired outcomes.

5. Need for the Study

Almost all of the clinical practice studies have either collected nutritional data from intermittent days or none at all because it is complicated and time intensive to obtain these data on a frequent, timely basis; although they are vital to prevent EUGR.

Without an accurate and frequent measurement of protein and energy delivery that is available on a nearly real-time basis, it is challenging to correlate the provision of early nutrition to growth outcomes. Electronic charting has provide an excellent resource but it is generally available for only the past 24 hours and does not provide a means to understand the development of growth over a period of time or correlate it to actual nutritional intakes of the infant. That is, electronic charting has highlighted a need to obtain and evaluate actual/delivered intakes at the point of care when the medical team is making nutritional decisions about changing the fluid and feeding regimens. Additionally, it is imperative that nurseries can evaluate not only trends of the individual infants but also the trends related to the clinical practices within their nurseries. The ability to review trends related to nutrition, feeding and growth will provide the necessary resources to develop and implement appropriate feeding protocols for macro nutrients as well as many essential trace elements.

Early adequate nutrition, even in the first hours after birth, is essential to prevent energy and protein deficits and growth outcomes that reflect lean body mass, lack of stunting in linear growth and appropriate brain growth. This study assessed the percentage of prescribed/intended and the percentage of A/D energy and protein intakes compared to Ziegler's guidelines. This knowledge is imperative for the neonatologist and medical team of P/I as well as A/D energy and protein in order to provide adequate nutrition in the critical first two weeks of life after birth. As demonstrated in several clinical practice studies, the education of the practitioner and the development of medical nutritional practices were instrumental in changing practice and improving positive growth outcomes.

6. Summary

The nutrition practices have advanced tremendously over the last 20 years for premature infants. Now practitioners are realizing that early nutrition, even the first few

hours after delivery, is essential to prevent long-term energy and protein deficits that may never be reversed and may result in serious consequences. A tremendous need exists for daily medical nutritional practices that assure the safe provision of adequate early nutrition and improved growth, development and longer neurodevelopmental and respiratory outcomes.

CHAPTER 3: METHODOLOGY

1. Overview

Study Design. An observational study of the feeding, nutrition and early growth of preterm infants was implemented in three tertiary care newborn intensive care units (NICUs): IU Health at Riley Hospital NICU, Methodist NICU and Indiana University NICU, Indianapolis, Indiana during July 2011 through mid February 2012. Approval by IRB for use of non-identifying data was obtained. Appendix B contains the IRB approvals. Participants did not have any changes in the routine clinical care provided during their course of stay in the NICU. Nutrition was prescribed by the Medical Team per existing protocols. Nutrition data (type of feedings, specialized recipes, volumes of IV fluids, EN and PN, and weights) were collected daily from existing medical records (nursing Input and Output "I and O" section).

2. Hypotheses

Central Hypothesis. The provision of adequate nutrition (energy and protein that meet Ziegler's theoretical estimated nutrient requirements) (18, 22) for VLBW infants during the first two weeks of life promotes earlier achievement of full enteral nutrition (EN) defined as 100 ±10 kcal/kg/day and improved growth outcomes at 36 weeks' post menstrual age (PMA).

The following specific aims and hypotheses evaluated the central hypothesis of the observational study:

Primary Aim. Assess nutrition (P/I and A/D energy and protein) relative to published guidelines during the first two weeks of life for VLBW infants in a tertiary care NICU.

Hypothesis 1: The percentage of the prescribed/intended energy (kcal/kg/day) intakes is significantly less than the recommended published guidelines (100% Ziegler's theoretical estimated energy requirements) for VLBW

infants during the first week, second week and average of the first two weeks after birth.

Hypothesis 2: The percentage of the prescribed/intended protein (g/kg/day) intakes is significantly less than the recommended published guidelines (100% of Ziegler's theoretical estimated protein requirements) for VLBW infants during the first week, second week and average of the first two weeks after birth.

Hypothesis 3: The percentage of the actual/delivered energy (kcal/kg/day) intakes is significantly less than the recommended published guidelines (100% of Ziegler's theoretical estimated energy requirements) for VLBW infants during the first week, second week and average of the first two weeks after birth.

Hypothesis 4: The percentage of the actual/delivered protein (g/kg/day) intakes is significantly less than the recommended published guidelines (100% Ziegler's theoretical estimated protein requirements) for VLBW infants during the first week, second week and average of the first two weeks after birth.

Secondary Aim 1. Correlate actual delivery of energy (kcal/kg/day) and protein (g/kg/day) intakes during the first week of life with DOL to reach 100 kcal/kg/day EN.

Hypothesis 1: The A/D energy (kcal/kg/day) intake for week 1 is not significantly correlated to DOL to reach 100 kcal/kg/day EN of VLBW infants.

Hypothesis 2: The A/D protein (g/kg/day) intake for week 1 is not significantly correlated to DOL to reach 100 kcal/kg/day EN of VLBW infants.

Secondary Aim 2. Evaluate the trends in nutritional data, i.e., determine correlation of A/D energy and protein intakes in the first weeks of life to DOL return to birth weight, compare growth velocity (from DOL on which 100 kcal/kg/day EN were

achieved to 36 weeks' PMA) to Ziegler's theoretical estimated fetal growth velocity and describe growth outcomes at 36 weeks' PMA.

Hypothesis 1: The A/D energy (kcal/kg/day) for week 1 is not significantly correlated to DOL return to birth weight.

Hypothesis 2: The A/D protein intake (g/kg/day) for week 1 is not significantly correlated to DOL return to birth weight.

Hypothesis 3: The growth velocity from DOL on which 100 kcal/kg/day EN were achieved to 36 weeks' PMA is not significantly different than Ziegler's theoretical estimates for fetal growth velocity.

Subjects. All preterm infants with a GA at birth of 30 weeks or less were enrolled from IU Health at Riley Hospital NICU, Methodist NICU and Indiana University NICU. Exclusions included infants with congenital anomalies or those who died during the first two weeks of life.

Measurements. Measurements included the following: P/I and A/D energy and protein intakes during the first 14 days after birth, days to 'return to birth weight', days to reach 100 kcal/kg/day EN and percentiles for weight at birth, DOL returned to birth weight and growth parameters at 36 weeks' PMA.

Study Procedures. Data collection began when preterm infants 30 weeks or less were admitted to the NICUs and continued until the infants were 36 weeks' PMA or discharged (or transferred) from the NICU, whichever occurred first. Participants continued with routine clinical care provided during their course of stay in the NICU. Nutrition was prescribed by the Medical Team per existing protocols. The EN and PN orders as *prescribed* intakes by physicians were obtained from the 'orders' section in the medical chart every 24 hours for each infant. The A/D amounts in milliliters of intravenous fluids, EN and/or PN for each infant were obtained from the 'input and output' section in the medical chart. Weights of infants without a diaper at birth and daily

weights were obtained at the same time each day with a digital electronic scale. The scales were calibrated with standards for accuracy on a yearly basis. Data were de-identified by removing all patient identifiers and Protected Health Information as defined by HIPPA and entered into an electronic system that calculated *P/I* and *A/D intakes* of energy (kcal/kg/day) and protein (g/kg/day) and growth velocity. The tool has been shown to be valid and reliable in calculating energy and protein intakes.

3. Statistical Analyses

Analyses were performed using SAS v9.3 (SAS Institute, Cary, NC). All model assumptions were verified before analyses were performed. Descriptive statistics were generated to show means, standard deviations, minimums and maximums.

Restatement of Hypotheses for Primary Aim. The prescribed/intended (P/I) and actual/delivered (A/D) energy intake (percentage theoretical estimated energy requirements, kcal/kg/day) and protein intakes (percentage theoretical estimated protein requirements, g/kg/day) is significantly less than 100% of the theoretical estimated nutrient requirements (18) for the first week, second week and average of the first two weeks for VLBW infants.

Analyses were performed to determine whether or not the mean percentages of P/I and A/D energy and protein were significantly different from Ziegler's theoretical estimated nutrient requirements. Raw differences were analyzed, with the hypothesis that the P/I or A/D values were significantly less than the theoretical estimated nutrient requirements. Student's t-tests were performed, for each individual DOL from one through fourteen and for weeks one and two. Bonferroni corrections were used to adjust for the multiple tests. To control for inflated type I errors; a modified p-value of 0.0015 was considered significant.

Analyses were performed also on the ratio of P/I or A/D to theoretical estimated nutrient requirements using a one sided test, testing against the hypothesis that the ratio

was 1 (or percent was 100%). Student's t-test was performed with a two-sided alternative, as the ratio could be either above or below 1. Bonferroni corrections were also used here, as in the previous section. Graphs were generated to visually show the differences and ratios, for both energy and protein.

Power Calculations. Based on preliminary data (see section 2. Statement of the Problem in Chapter 1), the mean observed energy intake was 59 kcal/kg/day with a *SD* of 16 for week 1 and a mean of 81 kcal/kg/day with a *SD* of 3 for week 2, which were used in the power calculations. Ziegler's theoretical estimated energy requirements are from 89 to 111 kcal/kg/day depending upon each infant's weight. Therefore, the study aimed to detect a difference in means ≥ 8 kcal/kg/day with a *SD* of 3. The required sample size of 39 infants was based upon a power level of more than 99% and an alpha level of 0.008. The alpha level was determined using the Bonferroni correction because two outcomes (i.e., energy and protein) were compared for 3 points in time (i.e., week 1, week 2 and weeks 1 - 2). The actual alpha level was controlled at 0.05 accounting for the multiple comparisons.

Based on the preliminary data (see section 2, Statement of the Problem in Chapter 1), the mean observed protein intake was 3.0 g/kg/day with a *SD* of 0.3 for week 1 and a mean of 3.2 g/kg/day with a *SD* of 0.1 for week 2, which were used in the power calculations. The recommended intake range is from 3 to 3.5 g/kg/day depending on each infant's weight. Therefore, we aimed to detect a difference in means ≥ 0.2 g/kg/day with a *SD* of 0.3. The required sample size of 39 infants was based on power level of more than 99% and an alpha level of 0.008. The alpha level was determined using the Bonferroni correction because two outcomes (i.e., energy and protein) were compared for 3 points in time (i.e., week 1, week 2 and weeks 1 - 2). The actual alpha level was controlled at 0.05 accounting for the multiple comparisons.

Restatement of Hypotheses for Secondary Aim 1. The A/D energy (percentage theoretical estimated energy requirements, kcal/kg/day) and protein (percentage theoretical estimated protein requirements, g/kg/day) intakes for week 1 are not significantly correlated to DOL to reach 100 kcal/kg/day EN of VLBW infants.

Regression analyses were performed to see if there was a significant association between the average amount of energy or protein actually given to infants during their first week of life, until the DOL of first full EN (described as within 10 kcal of 100 kcal/kg/day). Multivariate regression methods were used to see if outcomes remained significant even after controlling for other variables, such as birth weight and gestational age. Kaplan-Meier graphs were generated to visually show the range of days that it took infants to reach first full EN. Proportional hazard models were used to test for differences between AGA and SGA groups, within the survival analyses.

Restatement of Hypotheses 1 and 2 for Secondary Aim 2. The A/D energy (percentage theoretical estimated energy requirements, kcal/kg/day) and protein (percentage theoretical estimated protein requirements, g/kg/day) intakes for week 1 are not significantly correlated to DOL return to birth weight.

Regression analyses were performed to see if there was a significant association between the average amount of energy or protein actually given to infants during their first week of life and the time to return to birth weight. Multivariate regression methods were used to see if outcomes remained significant even after controlling for other variables, such as birth weight and gestational age.

Restatement of Hypothesis 3 for Secondary Aim 2. The growth velocity from DOL to reach 100 kcal/kg/day EN to 36 weeks' PMA was not significantly different than Ziegler's theoretical estimated fetal growth velocity.

Analyses were performed to determine whether or not the mean growth velocity from DOL to reach 100 kcal/kg/day EN to 36 weeks' PMA was significantly different from

Ziegler's theoretical estimated growth velocity. Raw differences were analyzed, with the null hypothesis that the difference between theoretical estimated growth velocity and actual growth velocity were zero and a two-sided alternative hypothesis, as differences, could be greater than or less than zero.

CHAPTER 4: RESULTS

1. Demographics

Forty infants (< 30 weeks gestational age (GA)) from July 2011 through mid February 2012 were included in the analyses for nutrition during the first two weeks of life, 40 in the correlation of early nutrition to DOL to return to birth weight; 39 in the correlation of early nutrition to DOL to reach full EN (one died) and 37 infants in the analyses of growth velocity and outcomes at 36 weeks' PMA (one died, two had not reached 36 weeks' PMA).

Table 4 summarizes the baseline and neonatal characteristics at birth by weight categories of the study population. Of the study infants, 40% weighed 501 - 700 g at birth (mean GA 25 weeks), 23% weighed 701 - 900 g at birth (mean GA 26 weeks), 35% weighed 901 - 1200 g at birth (mean GA 28 weeks) and 3% (1 infant) weighed 1201 - 1500 g at birth (30 weeks GA). Thirty infants were appropriate for gestational age (AGA) and ten infants were small for gestational age (SGA). One infant died at DOL 31.

Table 4. Subject baseline and neonatal characteristics of VLBW infants (n = 40)

Parameter	Body Weight, g				
	501 - 700	**701 - 900**	**901 - 1200**	**1201 - 1500**	**Total**
Sample Size	16 (40%)	9 (22.5%)	14 (35%)	1 (2.5%)	40 (100%)
Appropriate for Gestational Age	10 (25%)	8 (20%)	11 (27.5%)	1 (2.5%)	30 (100%)
Small for Gestational Age	6 (15%)	1 (2.5%)	3 (7.5%)	0	10 (25%)
Gestational Age Mean (Min - Max)	25 (23 - 28)	26 (24 - 28)	28 (26 - 29)	30 (30)	27 (23 - 30)
Gestational Age Median	24.8	25.1	28.4	29.6	26.4
Male (%)	9 (56%)	5 (56%)	10 (71%)	0 (0%)	24 (60%)
Twin Births	4 (25%)	0%	0%	0%	4 (10%)
Prenatal Steroids	13 (81%)	6 (67%)	5 (36%)	1 (100%)	25 (63%)
Intrapartum Antibiotics	7 (44)%	2 (22%)	3 (21%)	1 (100%)	13 (33%)
Mechanical Ventilation (> 7 Days)	13 (81%)	5 (56%)	4 (29%)	0	22 (55%)
Died (> 30 Days)	1 (6%)	0	0	0	1 (3%)

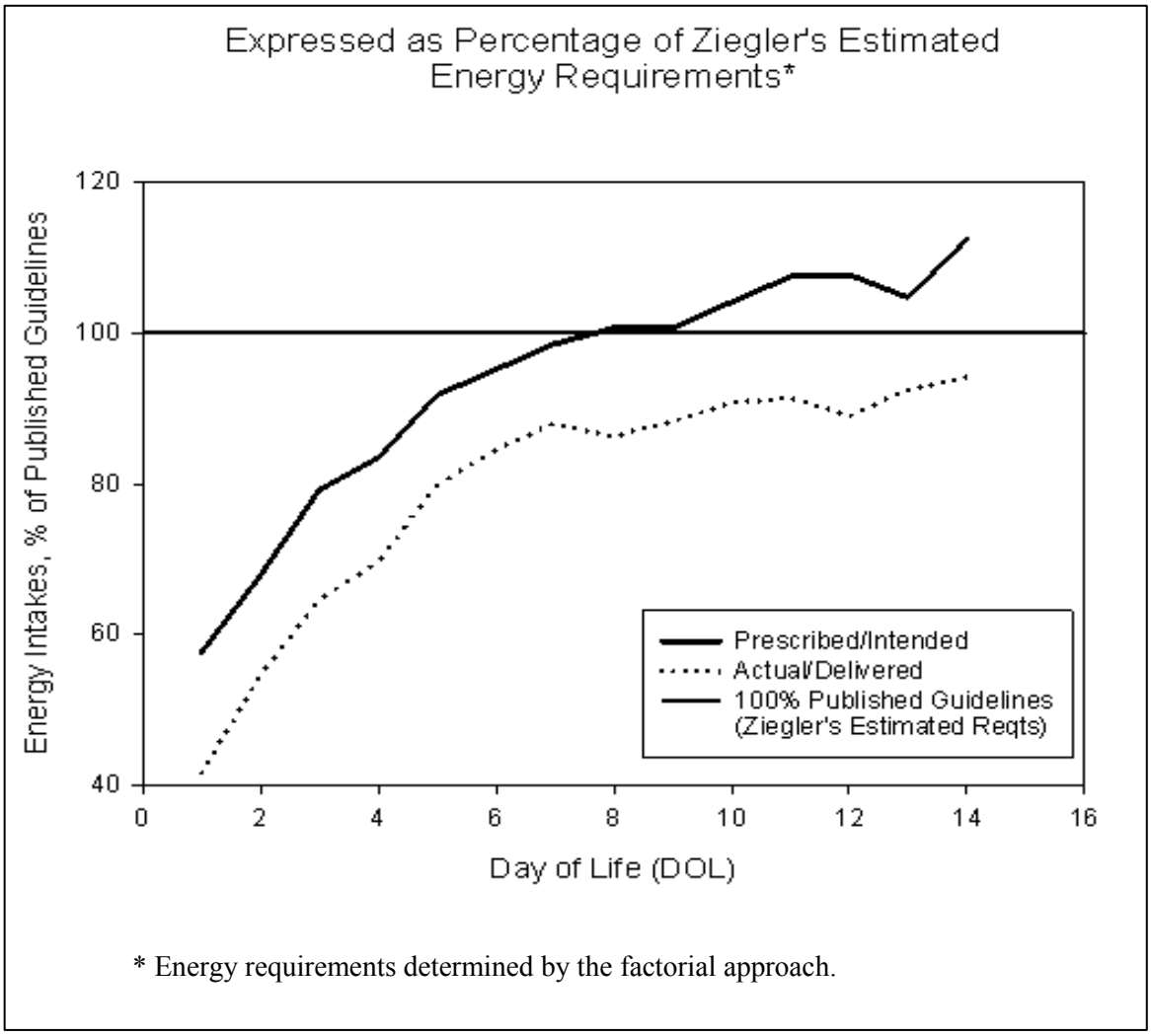
2. Energy and Protein Compared to Ziegler's Theoretical Estimated Requirements during the First Two Weeks of Life

Energy. Energy intakes (P/I and A/D) were calculated as the total energy from PN, IV Dextrose, and EN for each infant. During the first week, PN provided more than 90% of the energy (only 16 kcal/kg/day from EN through DOL 8). During the second week EN was gradually increased while PN was decreased. Figure 5 illustrates the percentages of the P/I and A/D energy intakes and Figure 6 illustrates the kcal/kg/day compared to Ziegler's theoretical estimated energy requirements. The average mean ±*SD* percentages of Ziegler's theoretical estimated energy requirements for P/I energy intakes during week 1, week 2 and both weeks were 82 ±22, 105 ±26 and 94 ±27 %, respectively (Table 5). The average ±*SD* percentages of Ziegler's theoretical estimated energy requirements for A/D week 1, week 2 and both weeks were 69 ±22, 90 ±20 and

80 ±24%, respectively (Table 5). For the first week and the average of the first two weeks of life, the P/I and A/D energy intakes were significantly *less* than 100% of Ziegler's theoretical estimated requirements ($p < 0.0001$, Table 5).

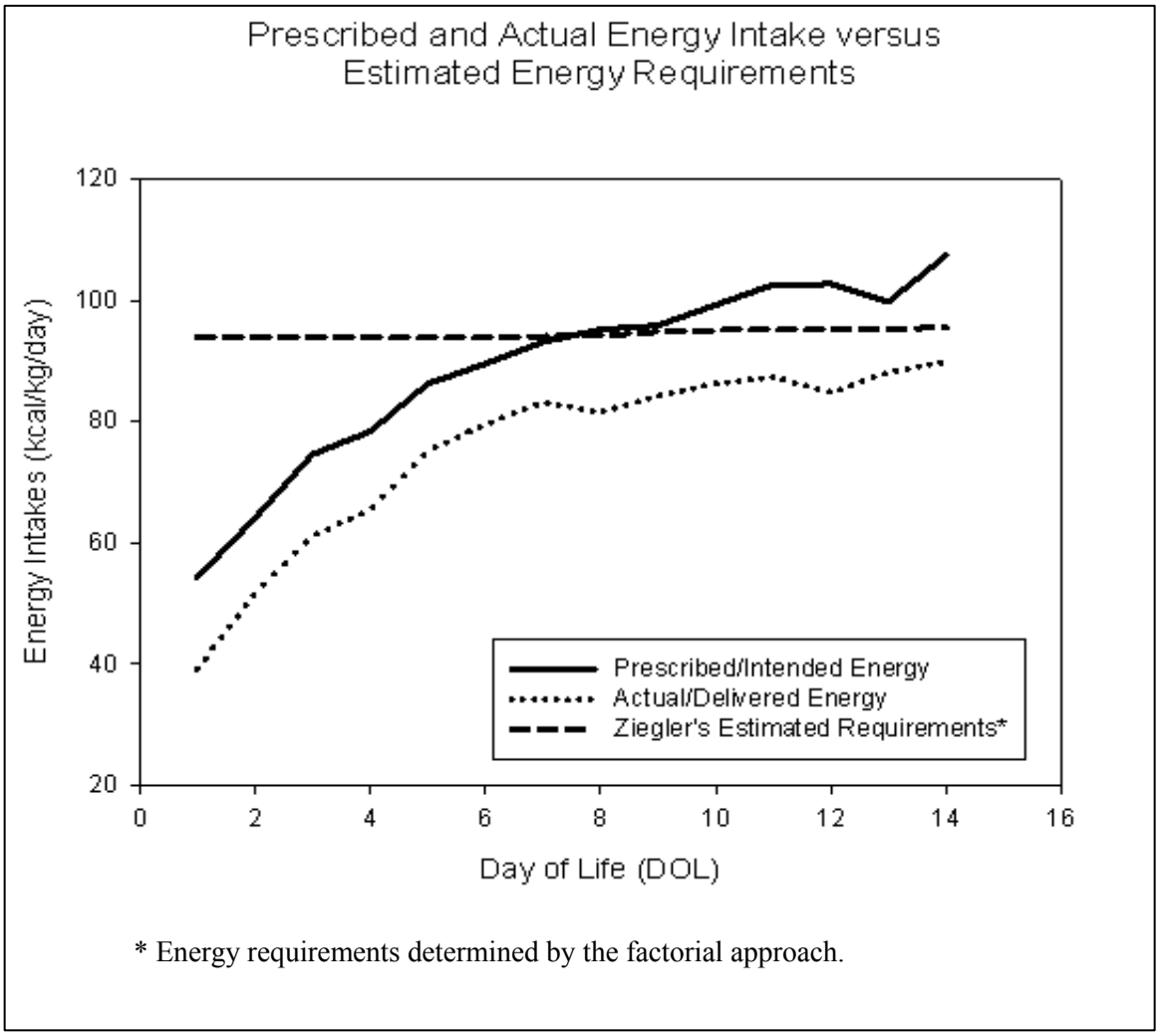
For the second week of life, the P/I was significantly *higher* than the theoretical estimated requirements (P/I, $p < 0.0006$); but the A/D was significantly *less* ($p \leq 0.0001$, Table 5). The average ±*SD* P/I energy intakes for week 1, week 2 and both weeks were 78 ±13, 100 ±19 and 89 ±15 kcal/kg/day (Table 6). The average ±*SD* A/D energy intakes for week 1, week 2 and both weeks were 65 ±16, 86 ±3 and 76 ±15 kcal/kg/day (Table 6). Similar to the percentages, the kcal/kg/day for the P/I and A/D energy intakes were significantly less than Ziegler's theoretical estimated requirements for the first week ($p < 0.0001$, Table 7) and the average of the first two weeks of life. Again, for the second week, the P/I energy (kcal/kg/day) was significantly higher ($p < 0.0006$) than Ziegler's theoretical estimated requirements but the A/D energy intakes (kcal/kg/day) were significantly lower ($p < 0.0001$, Table 7). Appendices C and D provide the statistical analyses for the percentage and kcal/kg/day differences in energy intakes from the theoretical estimated requirements. Although the numbers of infants in weight categories were not enough to complete statistical analyses, Appendix E provides the mean ±*SD* P/I and A/D intakes of energy within birth weight categories.

Figure 5. Mean energy intakes as a percentage of Ziegler's theoretical estimated energy requirements of VLBW infants



* Energy requirements determined by the factorial approach.

Figure 6. Mean energy intakes as kcal/kg/day compared to Ziegler's theoretical estimated energy intakes of VLBW infants



* Energy requirements determined by the factorial approach.

Table 5. Mean energy intakes as a percentage of Ziegler's theoretical estimated energy requirements of VLBW infants

Time Period (Day of Life)	Percentage of P/I Energy[1] Mean ±*SD* Min - Max	*p*-value of Percentage of P/I Energy	Percentage of A/D Energy[1] Mean ±*SD* Min - Max	*p*-value of Percentage of A/D Energy
1	58 (16) 0 - 97	< 0.0001*	42 (10) 17 - 85	< 0.0001*
2	68 (17) 0 - 98	< 0.0001*	55 (15) 1 - 81	< 0.0001*
3	79 (19) 45 - 129	< 0.0001*	65 (18) 24 - 107	< 0.0001*
4	83 (19) 40 - 114	< 0.0001*	70 (19) 31 - 107	< 0.0001*
5	98 (16) 58 - 126	0.0025	80 (14) 51 - 118	< 0.0001*
6	95 (17) 51 - 130	0.0834	84 (18) 49 - 115	< 0.0001*
7	99 (20) 61 - 139	0.6611	88 (19) 48 - 125	0.0002*
8	101 (19) 70 - 137	0.8229	86 (20) 32 - 126	< 0.0001*
9	101 (22) 59 - 148	0.8458	88 (21) 41 - 125	0.0013*
10	104 (21) 73 - 157	0.2208	91 (16) 56 - 120	0.0010*
11	108 (24) 73 - 176	0.0593	91 (19) 44 - 135	0.0078
12	108 (29) 38 - 169	0.1033	89 (23) 24 - 131	0.0047
13	105 (29) 51 - 183	0.3083	93 (19) 49 - 129	0.0153
14	112 (34) 62 - 206	0.0253	94 (21) 58 - 150	0.0821
Week 1 (Days 1 - 7)	82 (22) 0 - 139	< 0.0001*	69 (22) 1 - 125	< 0.0001*
Week 2 (Days 8 - 14)	105 (26) 38 - 206	0.0006*	90 (20) 24 - 150	< 0.0001*
Overall (Days 1 - 14)	94 (27) 0 - 206	< 0.0001*	80 (24) 1 - 150	< 0.0001*

Abbreviations: A/D = actual/delivered; P/I = prescribed/intended.

[1] Percentage of prescribed and actual values were calculated compared to Ziegler's theoretical estimated energy requirements.

* Indicates a significant difference at a Bonferroni adjusted alpha level of 0.05 (adjusted *p*-value = 0.0015), for a one-sided t-test with a hypothesis that the percentage is 100.

Table 6. Mean energy intakes as kcal/kg/day compared to Ziegler's estimated energy intakes of VLBW infants

Time Period (Day of Life)	Prescribed/Intended Energy (kcal/kg/day)[1] Mean ±*SD* Median, Min - Max	Actual/Delivered Energy (kcal/kg/day)[1] Mean ±*SD* Median, Min - Max	Ziegler Theoretical Estimated Energy Requirements (kcal/kg/day)
1	56 (13.6) 56 (46 - 66)	39 (10.46) 38 (35 - 43)	89 - 108
2	66 (13.8) 65 (56 - 75)	53 (12.60) 52 (47 - 60)	89 - 108
3	75 (18.49) 73 (62 - 87)	61 (18.77) 61 (48 - 73)	89 - 108
4	79 (19.65) 82 (63 - 95)	65 (18.99) 66 (50 - 79)	89 - 108
5	86 (16.19) 87 (73 - 100)	75 (15.67) 71 (65 - 83)	89 - 108
6	90 (17.47) 89 (76 - 105)	80 (18.05) 82 (65 - 96)	89 - 108
7	93 (21.42) 92 (76 - 110)	83 (20.07) 79 (71 - 98)	89 - 108
8	95 (21.18) 94 (77 - 113)	81 (20.54) 79 (66 - 96)	89 - 108
9	96 (24.10) 93 (77 - 115)	84 (22.61) 88 (69 - 101)	89 - 108
10	99 (23.09) 95 (81 - 110)	86 (17.06) 85 (74 - 98)	89 - 108
11	103 (26.57) 95 (84 - 118)	87 (20.52) 82 (72 - 103)	89 - 108
12	103 (29.42) 10 (82 - 112)	85 (22.63) 87 (69 - 105)	89 - 108
13	100 (28.34) 97 (79 - 114)	88 (18.59) 89 (76 - 105)	89 - 108
14	108 (32.94) 98 (83 - 130)	90 (21.22) 85 (75 - 106)	89 - 108
Week 1 (Days 1 - 7)	78 (13.43) 79 (66 - 90)	65 (15.67) 65 (53 - 80)	89 - 108
Week 2 (Days 8 - 14)	100 (18.92) 100 (96 - 103)	86 (2.83) 86 (84 - 88)	89 - 108
Overall (Days 1 - 14)	89 (15.17) 94 (78 - 101)	76 (15.27) 82 (64 - 87)	89 - 108

[1] Values are means ±*SD*; medians, (25^{th} percentile - 75^{th} percentile)

Table 7. Differences in mean energy intakes as kcal/kg/day compared to Ziegler's theoretical estimated energy intakes of VLBW infants

Time Period (Day of Life)	Theoretical Estimated Energy Minus P/I Energy[1] Mean ±*SD* Min - Max	*p*-value of Theoretical Estimated Energy Minus P/I Energy	Theoretical Estimated Energy Minus A/D Energy[1] Mean ±*SD* Min - Max	*p*-value of Theoretical Estimated Energy Minus A/D Energy
1	39.7 (15.1) 3.3 - 89.0	< 0.0001*	55 (10.6) 15.0 - 84.0	< 0.0001*
2	29.9 (14.9) 1.8 - 89.0	< 0.0001*	42.4 (13.0) 19.0 - 88.0	< 0.0001*
3	19.4 (17.3) 26.5 - 48.6	< 0.0001*	32.8 (16.3) -7.4 - 67.4	< 0.0001*
4	15.5 (17.9) 12.8 - 53.2	< 0.0001*	28.5 (18.4) -5.9 - 63.0	< 0.0001*
5	7.6 (14.8) 23.1 - 37.8	0.0024	18.7 (13.4) -18.0 - 43.8	< 0.0001*
6	4.4 (15.7) 26.7 - 43.2	0.0872	14.4 (16.3) -14.6 - 45.0	< 0.0001*
7	0.9 (18.7) 37.1 - 34.9	0.7556	10.9 (17.4) -24.9 - 46.3	0.0003*
8	-1.0 (18.3) 37.1 - 27.1	0.7204	12.6 (18.5) -23.5 - 68.7	0.0001*
9	-1.1 (21.3) 52.2 - 36.6	0.7501	10.6 (19.7) -24.9 - 52.5	0.0015*
10	-4.2 (20.9) 61.8 - 28.7	0.2120	8.8 (16.0) -20.3 - 46.3	0.0012*
11	-7.4 (24.4) 81.7 - 27.4	0.0613	7.8 (18.2) -32.3 - 49.5	0.0095
12	-7.6 (28.1) 70.1 - 55.4	0.0960	10.4 (21.5) -27.5 - 67.5	0.0040
13	-4.5 (27.5) 76.6 - 43.4	0.3042	7.1 (17.5) 27.1 - 45.5	0.0141
14	-11.9 (32.2) 97.5 - 37.8	0.0247	5.6 (20.1) -45.7 - 42.8	0.0875
Week 1 (Days 1 - 7)	16.6 (20.8) 37.1 - 89.0	< 0.0001*	28.7 (21.1) -24.9 - 88.0	< 0.0001*
Week 2 (Days 8 - 14)	-5.4 (25.1) 97.5 - 55.4	0.0004*	9.0 (18.8) -45.7 - 68.7	< 0.0001*
Overall (Days 1 - 14)	5.6 (25.5) 97.5 - 89.0	< 0.0001*	18.8 (22.2) -45.7 - 88.0	< 0.0001*

Abbreviations: A/D = actual/delivered; P/I = prescribed/intended.

[1] Differences were calculated as Ziegler's theoretical estimated energy requirements minus the prescribed/intended or actual/delivered energy intakes.

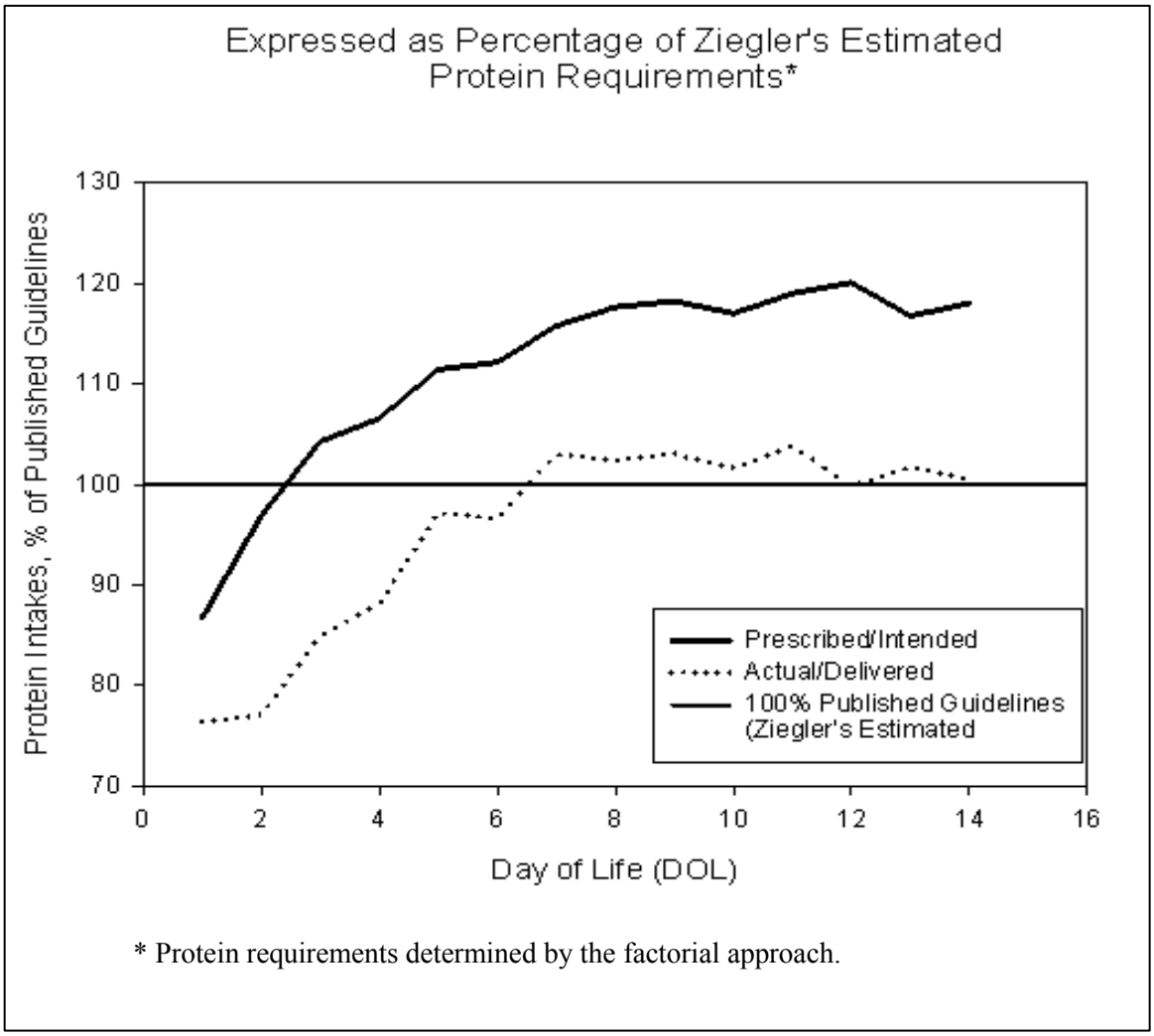
* Indicates a significant difference at a Bonferroni adjusted alpha level of 0.05 (adjusted *p*-value = 0.0015), for a two-sided t-test with a null hypothesis that the difference is 0.

Protein. Protein intakes (P/I and A/D) were calculated as the total protein from PN and EN for each infant. During the first week, PN provided approximately 93% of the protein beginning DOL 3 (only 0.2 g/kg/day from EN) through DOL 8; during the second week EN is gradually increased while PN was decreased. Figure 7 illustrates the percentages of the P/I and A/D protein intakes and Figure 8 illustrates the g/kg/day intakes compared to Ziegler's theoretical estimated protein requirements. The average ±*SD* percentages of Ziegler's theoretical estimated protein requirements for P/I energy intakes during week 1, week 2 and both weeks were 105 ±18, 118 ±22 and 112 ±21%, respectively (Table 8). The average ±*SD* percentages of Ziegler's theoretical estimated protein requirements for A/D week 1, week 2 and both weeks for A/D were 89 ±20, 102 ±22 and 96 ±22%, respectively (Table 8).

For the first week, second week and average of the first two weeks of life, the P/I protein as percentages of Ziegler's theoretical estimated nutrient requirements and g/kg/day were significantly higher ($p < 0.0001$, Tables 8 and 9) than Ziegler's theoretical estimated protein requirements; however, the A/D protein as percentage of Ziegler's theoretical estimated protein requirements and g/kg/day differences were significantly lower for the first week of life and the average of the first two weeks. For the second week of life, the A/D protein intakes as percentage of Ziegler's theoretical estimated protein requirements and g/kg/day intakes were not significantly different from the Ziegler's theoretical estimated protein requirements (Tables 8 and 9). The average ±*SD* P/I protein intakes for week 1, week 2 and both weeks were 3.5 ±0.56, 4.1 ±0.04 and 3.8 ±0.51 g/kg/day, respectively (Table 10). The average ±*SD* A/D protein intakes for week 1, week 2 and both weeks were 3.1 ±0.38, 3.5 ±0.09 and 3.3 ±0.09 g/kg/day (Table 10). Appendices F and G provide the statistical analyses for the percentage of theoretical estimates and g/kg/day differences in protein intakes from Ziegler's

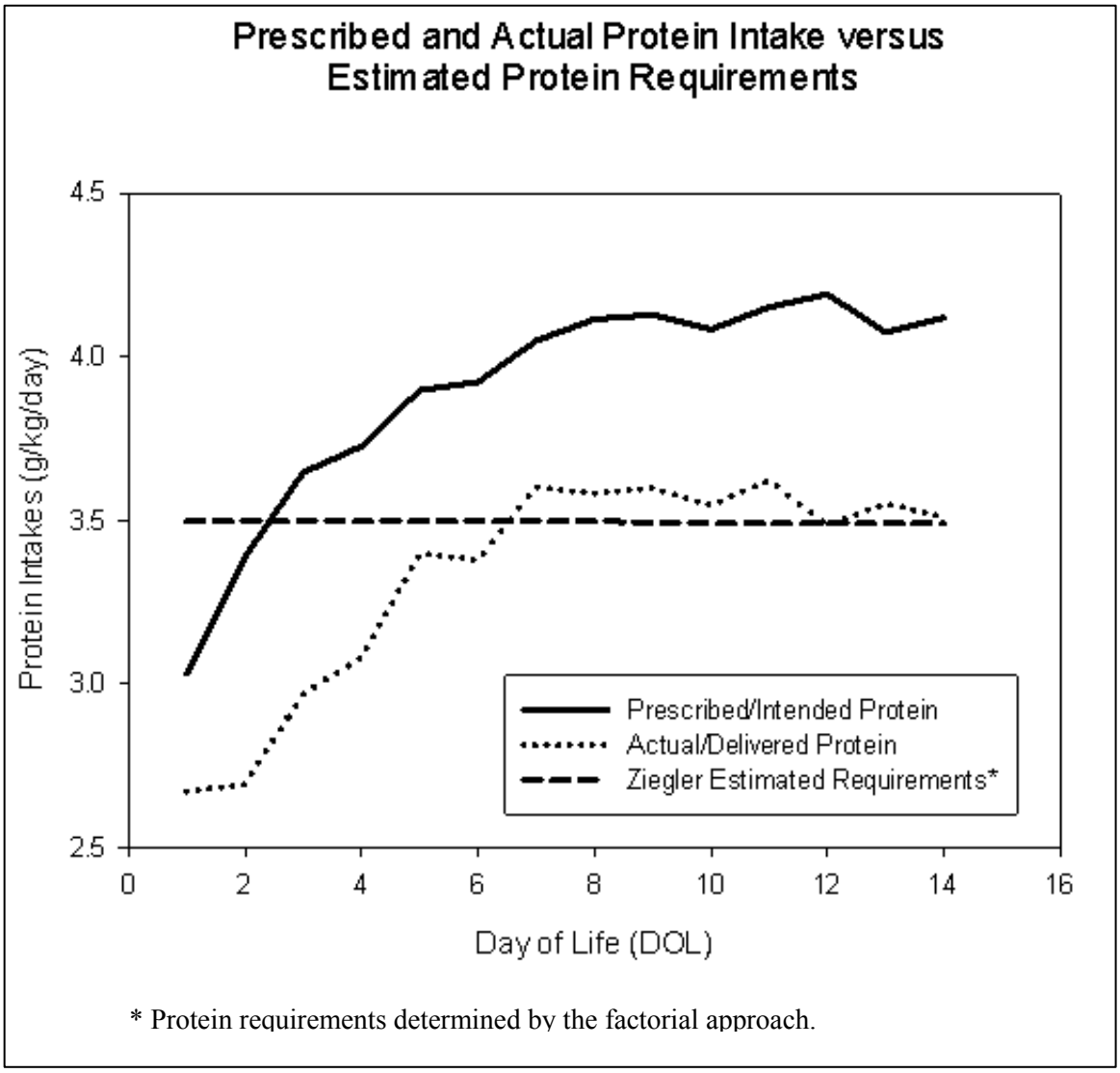
theoretical estimated requirements. Appendix E provides the means ±*SD* P/I and A/D intakes of protein within birth weight categories.

Figure 7. Mean protein intakes as a percentage of Ziegler's theoretical estimated protein requirements of VLBW infants



* Protein requirements determined by the factorial approach.

Figure 8. Mean protein intakes as g/kg/day compared to Ziegler's theoretical estimated protein intakes of VLBW infants



* Protein requirements determined by the factorial approach.

Table 8. Mean protein intakes as a percentage of Ziegler's theoretical estimated protein requirements of VLBW infants

Time Period (Day of Life)	Percentage of P/I Protein[1] Mean ±*SD* Min - Max	p-value of Percentage of P/I Protein	Percentage of A/D Protein[1] Mean ±*SD* Min - Max	*p*-value of Percentage of A/D Protein
1	87 (22) 0 - 106	0.0005*	76 (14) 28 - 95	< 0.0001*
2	97 (19) 0 - 123	0.3044	77 (20) 24 - 117	< 0.0001*
3	104 (11) 86 - 126	0.0235	85 (20) 28 - 123	< 0.0001*
4	107 (13) 73 - 132	0.0020	88 (20) 46 - 125	0.0006*
5	111 (13) 80 - 132	< 0.0001*	97 (16) 50 - 121	0.2547
6	112 (13) 86 - 136	< 0.0001*	97 (19) 54 - 124	0.2771
7	116 (1) 86 - 153	< 0.0001*	103 (16) 63 - 136	0.2496
8	118 (15) 88 - 162	< 0.0001*	102 (22) 19 - 142	0.5016
9	118 (15) 93 - 149	< 0.0001*	103 (18) 57 - 138	0.2992
10	117 (20) 41 - 173	< 0.0001*	102 (21) 35 - 131	0.6325
11	119 (22) 86 - 187	< 0.0001*	104 (25) 36 - 154	0.3363
12	120 (25) 81 - 188	< 0.0001*	100 (22) 24 - 145	0.9578
13	117 (25) 67 - 190	0.0001*	102 (20) 21 - 141	0.5758
14	118 (32) 34 - 196	0.0009*	101 (24) 30 - 141	0.8950
Week 1 (Days 1 - 7)	105 (18) 0 - 153	< 0.0001*	89 (20) 24 - 136	< 0.0001*
Week 2 (Days 8 - 14)	118 (22) 34 - 196	< 0.0001*	102 (22) 19 - 154	0.1531
Overall (Days 1 - 14)	112 (21) 0 - 196	< 0.0001*	96 (22) 19 - 154	< 0.0001*

Abbreviations: A/D = actual/delivered; P/I = prescribed/intended.

[1] Percentage of prescribed and actual values was calculated compared to Ziegler's theoretical estimated protein requirements.

* Indicates a significant difference at a Bonferroni adjusted alpha level of 0.05 (adjusted *p*-value = 0.0015), for a one-sided t-test with a null hypothesis that the percentage is 100. Percentage was calculated as P/I or A/D divided by Ziegler's theoretical estimated protein requirement.

Table 9. Differences in mean protein intakes as g/kg/day compared to Ziegler's theoretical estimated protein intakes of VLBW infants

Time Period (Day of Life)	Theoretical Estimated Protein Minus P/I Protein[1] Mean ±*SD* Min - Max	*p*-value of Theoretical Estimated Protein Minus P/I Protein	Theoretical Estimated Protein Minus A/D Protein[1] Mean ±*SD* Min - Max	*p*-value of Theoretical Estimated Protein Minus A/D Protein
1	0.47 (0.77) -0.22 - 3.50	0.0005*	0.83 (0.50) 0.19 - 2.53	< 0.0001*
2	0.11 (0.65) -0.80 - 3.50	0.3021	0.80 (0.70) -0.60 - 2.67	< 0.0001*
3	-0.15 (0.39) -0.87 - 0.50	0.0237	0.53 (0.70) -0.81 - 2.51	< 0.0001*
4	-0.23 (0.44) -1.11 - 0.96	0.0020	0.42 (0.70) -0.85 - 1.90	0.0005*
5	-0.40 (0.46) -1.11 - 0.70	< 0.0001*	0.10 (0.54) -0.72 - 1.73	0.2518
6	-0.43 (0.44) -1.27 - 0.50	< 0.0001*	0.12 (0.68) -0.83 - 1.62	0.2749
7	-0.55 (0.50) -1.85 - 0.50	< 0.0001*	-0.11 (0.57) -1.27 - 1.29	0.2505
8	-0.62 (0.51) -2.16 - 0.41	< 0.0001*	-0.08 (0.78) -1.49 - 2.82	0.5041
9	-0.64 (0.51) -1.73 - 0.25	< 0.0001*	-0.11 (0.64) -1.32 - 1.50	0.3049
10	-0.59 (0.71) -2.47 - 2.01	< 0.0001*	-0.06 (0.72) -1.06 - 2.20	0.6271
11	-0.66 (0.76) -2.97 - 0.50	< 0.0001*	-0.13 (0.86) -1.88 - 2.26	0.3397
12	-0.70 (0.88) -3.08 - 0.66	< 0.0001*	0.01 (0.77) -1.66 - 2.64	0.9594
13	-0.59 (0.87) -3.15 - 1.16	0.0001*	-0.06 (0.68) -1.45 - 2.75	0.5722
14	-0.63 (1.11) -3.36 - 2.31	0.0009*	-0.02 (0.84) -1.45 - 2.46	0.8919
Week 1 (Days 1 - 7)	-0.17 (0.62) -1.85 - 3.50	< 0.0001*	0.38 (0.71) -1.27 - 2.67	< 0.0001*
Week 2 (Days 8 - 14)	-0.63 (0.78) -3.36 - 2.31	< 0.0001*	-0.06 (0.75) -1.88 - 2.82	0.1537
Overall (Days 1 - 14)	-0.40 (0.74) -3.36 - 3.50	< 0.0001*	0.15 (0.76) -1.88 - 2.82	< 0.0001*

Abbreviations: A/D = actual/delivered; P/I = prescribed/intended.

[1] Differences were calculated as Ziegler's theoretical estimated protein requirements minus the prescribed or actual protein intakes.

* Indicates a significant difference at a Bonferroni adjusted alpha level of 0.05 (adjusted *p*-value = 0.0015), for a two-sided t-test with a null hypothesis that the difference is 0.

Table 10. Mean protein intakes as g/kg/day compared to Ziegler's estimated protein intakes of VLBW infants

Time Period (Day of Life)	Prescribed/Intended Protein (g/kg/day)[1] Mean ±*SD* Median, Min - Max	Actual/Delivered Protein (g/kg/day)[1] Mean ±*SD* Median, Min - Max	Ziegler Theoretical Estimated Protein Requirements (g/kg/day)
1	3.1 (0.35) 3.0 (3.0 - 3.5)	2.6 (0.65) 2.8 (2.5 - 3.0)	3.4 - 3.5
2	2.6 (0.66) 2.8 (2.4 - 3.2)	2.7 (0.69) 2.8 (2.4 - 3.2)	3.4 - 3.5
3	3.0 (0.70) 3.0 (2.5 - 3.5)	3.0 (0.70) 3.0 (2.5 - 3.5)	3.4 - 3.5
4	3.7 (0.44) 3.6 (3.5 - 4.0)	3.1 (0.70) 3.1 (2.7 - 3.5)	3.4 - 3.5
5	3.9 (0.46) 4.0 (3.5 - 4.3)	3.4 (0.54) 3.5 (3.0 - 3.9)	3.4 - 3.5
6	3.9 (0.44) 4.0 (3.5 - 4.3)	3.4 (0.68) 3.5 (2.8 - 4.0)	3.4 - 3.5
7	4.1 (0.50) 4.0 (3.6 - 4.5)	3.6 (0.57) 3.7 (3.3 - 4.0)	3.4 - 3.5
8	4.1 (0.52) 4.2 (3.8 - 4.5)	3.6 (0.78) 3.7 (3.1 - 4.1)	3.4 - 3.5
9	4.1 (0.50) 4.2 (3.7 - 4.5)	3.6 (0.64) 3.7 (3.3 - 4.0)	3.4 - 3.5
10	4.1 (0.71) 4.0 (3.8 - 4.5)	3.6 (0.72) 3.7 (3.1 - 4.1)	3.4 - 3.5
11	4.2 (0.75) 4.0 (3.6 - 4.5)	3.6 (0.86) 3.7 (3.2 - 4.1)	3.4 - 3.5
12	4.2 (0.89) 4.0 (3.5 - 4.5)	3.4 (0.93) 3.5 (3.1 - 3.8)	3.4 - 3.5
13	4.1 (0.87) 4.0 (3.5 - 4.3)	3.6 (0.68) 3.6 (3.3 - 3.9)	3.4 - 3.5
14	4.1 (1.11) 4.0 (3.5 - 4.6)	3.5 (0.85) 3.7 (3.1 - 4.1)	3.4 - 3.5
Week 1 (Days 1 - 7)	3.5 (0.56) 3.7 (3.0 - 3.9)	3.1 (0.38) 3.1 (2.7 - 3.4)	3.4 - 3.5
Week 2 (Days 8 - 14)	4.1 (0.04) 4.1 (4.1 - 4.2)	3.5 (0.09) 3.6 (3.5 - 3.6)	3.4 - 3.5
Overall (Days 1 - 14)	3.8 (0.51) 4.1 (3.6 - 4.1)	3.3 (0.09) 3.4 (3.1 - 3.6)	3.4 - 3.5

1 Values are means ±*SD*; medians, (25^{th} percentile - 75^{th} percentile)

3. Early Nutrition (First Week of Life) and the Infant's Ability to Reach 100 kcal/kg/day Enteral Nutrition

The A/D energy intakes (kcal/kg/day) for the first week of life were significantly correlated to the number of days (DOL) to reach full EN defined as 100 ±10 kcal/kg/day from enteral nutrition in 39 VLBW infants (Pearson Coefficient -0.3220, *p* value = 0.0456, Figure 9). As the A/D energy increased during the first week of life, the number of days of life until full EN was reached decreased, consistent with the hypothesis. With multivariate regression analyses that adjusted for body weight, the increased energy intakes still were associated with fewer days to reach full EN. Body weight also was significantly associated with days to reach full EN, i.e., the lower the weight of the infant, the fewer number of days to reach 100 kcal/kg/day. The multivariate regression equation is the following: Number of days to reach 100 kcal/kg/day = -0.5952 (energy, $p < 0.0001$) + 0.5827 (body weight, $p < 0.0001$). The A/D protein (g/kg/day) during the first week of life was not correlated with the number of days to reach full EN (Pearson Coefficient, $p = 0.6725$). Appendix H provides the correlation analyses of the A/D energy and protein during the first week to the number of days to reach full EN. Figure 10 illustrates the distribution of the DOL the infants reached 100 kcal/kg/day EN. Fifty percent of the babies reached 100 kcal/kg/day on DOL 23 (median) and 75% reached 100 kcal/kg/day by 31 days (Figure 10).

Figure 9. Relationship of A/D energy to the day of life (DOL) when VLBW infants reached full enteral feedings (100 kcal/kg/day)

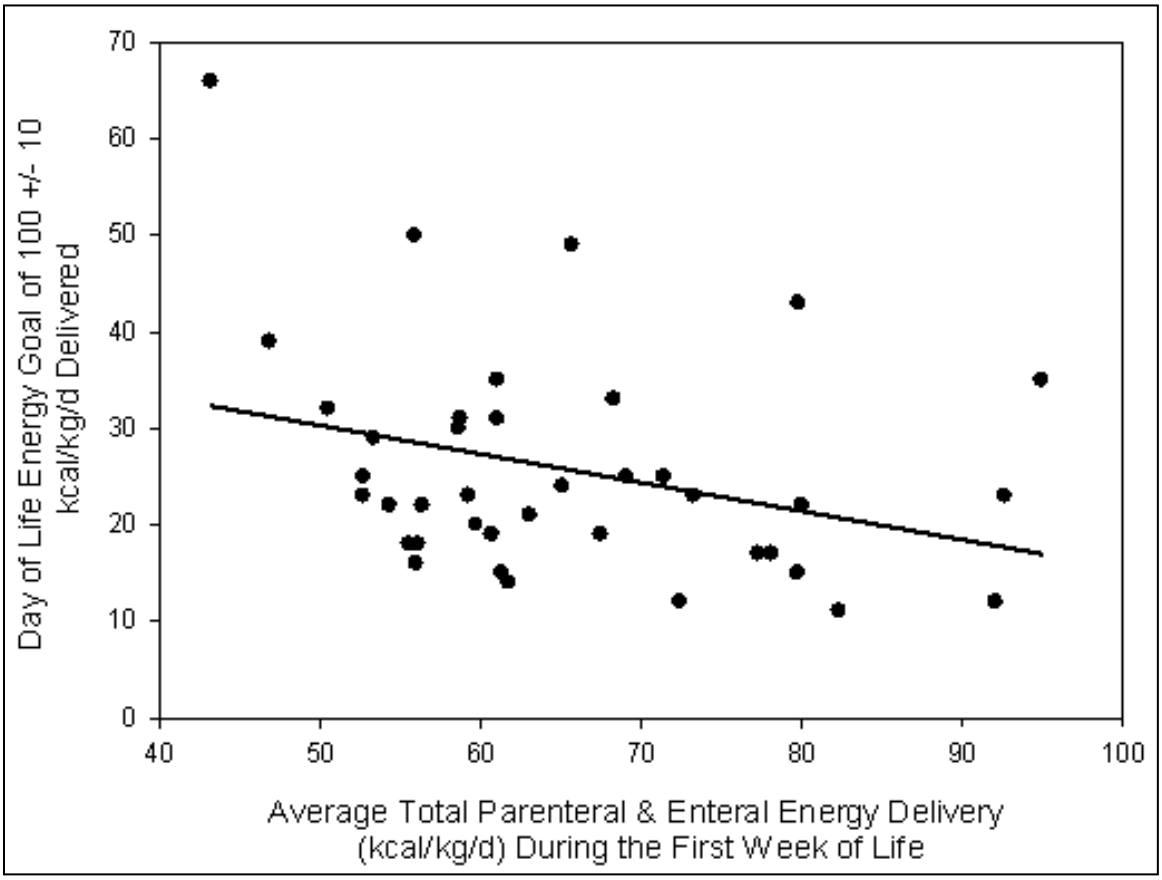
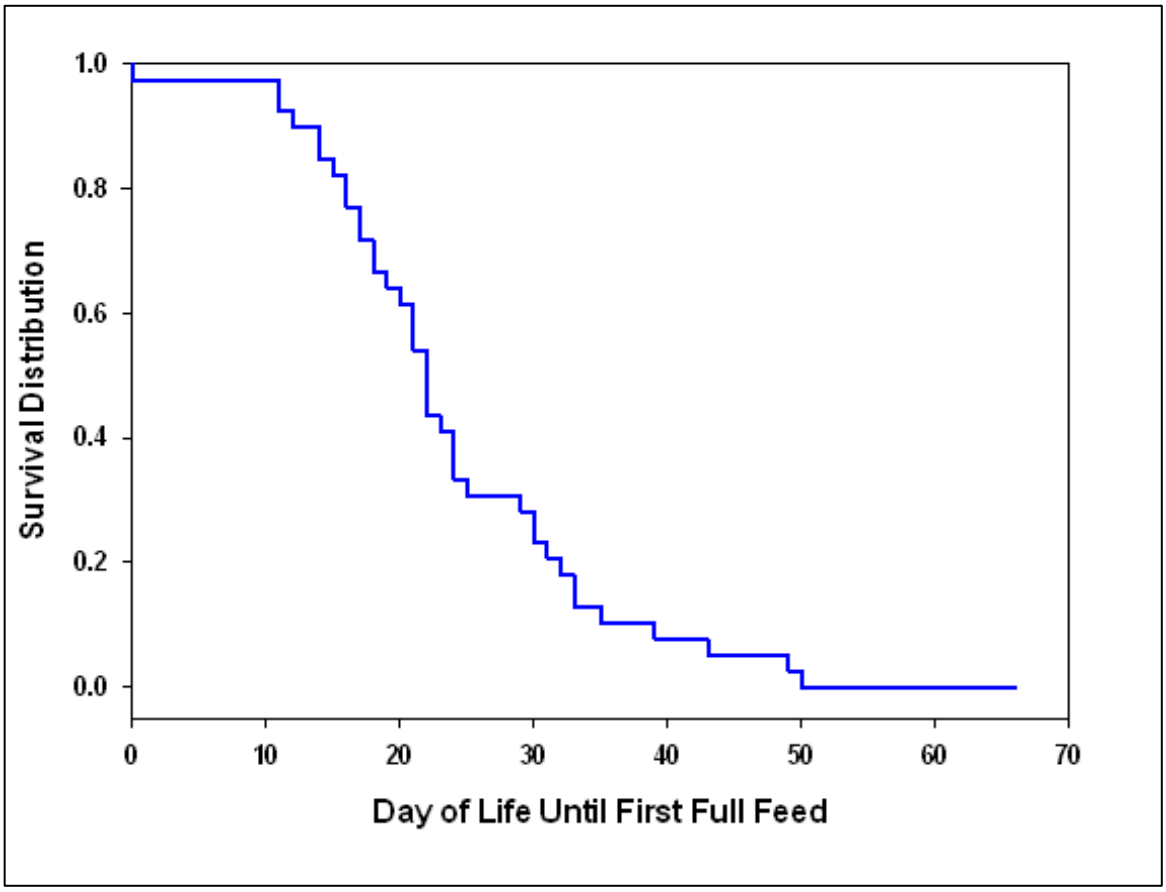


Figure 10. Distribution of days of life (DOL) when VLBW infants reached full enteral feedings (100 kcal/kg/day)



4. Early Nutrition (First Week of Life), Growth Milestones and Growth Outcomes at 36 weeks' PMA

Table 11 summarizes the growth milestones i.e., DOL return to birth weight and DOL reached full EN defined as100 kcal/kg/day for all infants, AGA/SGA and birth weight categories. The mean ±*SD* DOL return to birth weight for all VLBW infants was 10 ±4 days; the mean DOL to reach full EN for all VLBW infants was 26 ±12 days. The SGA infants returned to birth weight (7 ±3 days, n = 10) significantly faster ($p = 0.0224$) than the AGA infants (11 ±4 days, n = 30). The numbers of infants in the different weight categories were too few to determine differences in time to return to birth weight within weight categories. The frequency distribution (number of infants) vs DOL to return to birth weight is shown in Figure 11 and frequency distribution vs DOL reached full EN in Figure 12. Fifteen (37.5%) VLBW infants returned to birth weight between 12 and 19 days (Figure 11) and thirteen (33%) VLBW infants reached full EN at DOL 30 or later (Figure 12).

The A/D energy (kcal/kg/day) and protein intakes (g/kg/day) in the first week of life were not significantly correlated to the time to return to birth weight; however, as indicated above, the energy but not protein intakes were significantly correlated to the time to reach full EN. Appendix H provides the average ±*SD* energy and protein intakes during the first week of life for the different birth weight categories.

The mean growth velocity as g/kg/day from the time to reach full EN to 36 weeks' PMA of 36 VLBW infants was significantly different ($p = 0.03$) from Ziegler's theoretical estimated fetal growth velocity. The mean ±*SD* growth velocity during this time period was 14.8 ±3.2 g/kg/day compared Ziegler's theoretical estimated growth velocity of 16.1 ±2.0 (Table 12).

Table 13 summarizes the number of infants in each of the percentiles for weights at birth, return to birth weights and weights at 36 weeks' PMA (Fenton premature infant growth grids). Numbers of infants in percentiles of the Lubchenco premature infant growth grid are given only for 36 weeks' PMA since they do not extend to birth weights as low as 500 g. On the Fenton grid, the standard premature infant growth grid used by institutions in this study, at birth 9 of 40 (22.5%) VLBW infants were < 10^{th} percentile (SGA infants) and at return to birth weight 16 of 40 (40%) were < 10^{th} percentile. On the Fenton grid, at 36 weeks' PMA, 20 of 40 (50%) VLBW infants were < 10^{th} percentile. On the Lubchenco growth grid, at 36 weeks' PMA, 13 of 38 (34%) were < 10^{th} percentile and 22 of 38 (58%) were between the 10^{th} and 50^{th} percentiles. Appendix I summarizes the number of infants by weight categories in each of the percentiles on the Fenton and Lubchenco growth grids.

Figure 11. Frequency Distribution of days of life (DOL) when VLBW infants returned to birth weight

Figure 12. Frequency Distribution of days of life (DOL) when VLBW infants reached full enteral feedings (100 kcal/kg/day)

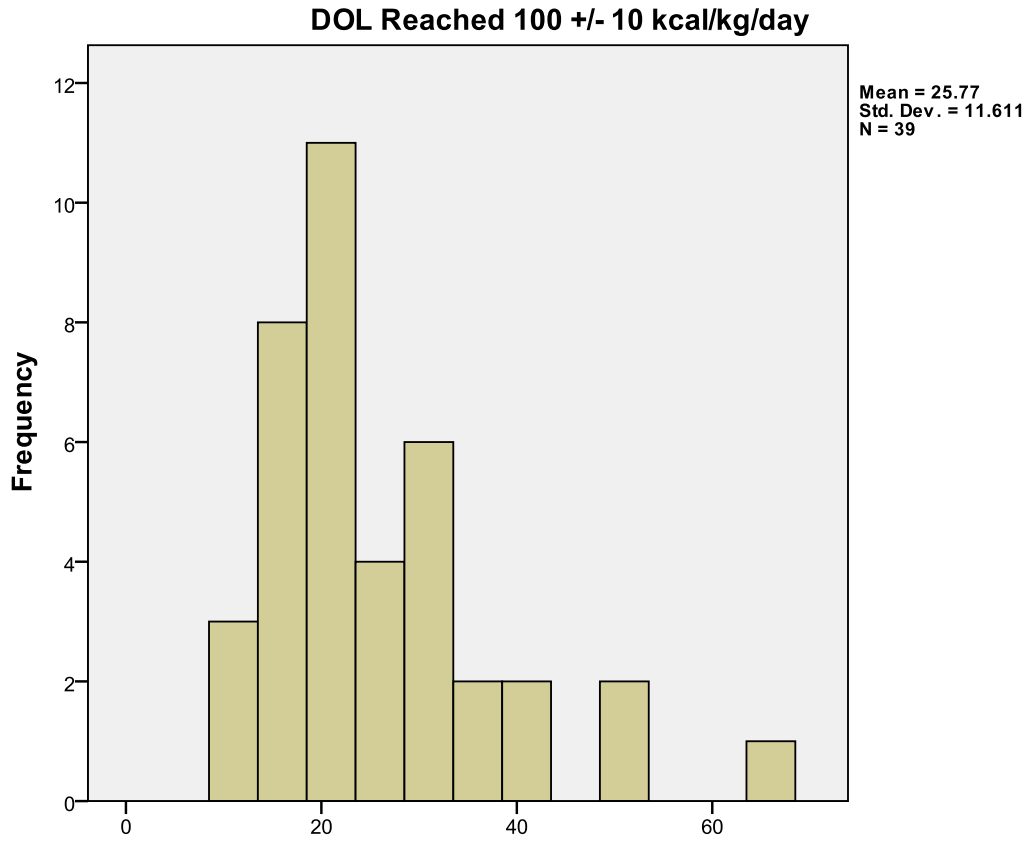


Table 11. Growth milestones for VLBW infants (n = 40)

Day of Life (DOL)	Body Weight, g				
	501 - 700	701 - 900	901 - 1200	1201 - 1500	Total
DOL Return to Birth Weight, AGA:					
Mean	9.4	12.9	10.6	10	10.8
(±*SD*)	(4.9)	(4.01)	(3.4)	(NA)	(4.16)
Number	n = 10	n = 8	n = 11	n = 1	n = 30
DOL Return to Birth Weight, SGA:					
Mean	6.7	9	8.3	NA	7.4
(±*SD*)	(3.6)	(NA)	(1.5)	(NA)	(2.95)
Number	n = 6	n = 1	n = 3	n = 0	n = 10
DOL Reached 100 ±10 kcal/kg, AGA:					
Mean	25.1	28.1	24	23	25.45
(±*SD*)	(7.4)	(16.7)	(10.3)	(NA)	(11.25),
Number	n = 9	n = 8	n = 11	n = 1	n = 29
DOL Reached 100 ±10 kcal/kg, SGA:					
Mean	26.5	43	21.7	NA	26.7
(±*SD*)	(13.6)	(NA)	(12.2)	(NA)	(13.2),
Number	n = 6	n = 1	n = 3	n = 0	n = 10

Abbreviation: NA = not applicable for standard deviation and/or mean for n = 0 or 1.

Table 12. Mean growth velocity (g/day, g/kg/day) compared to Ziegler's theoretical estimated growth velocity of VLBW infants (n = 37)

Growth Velocity	Actual Growth from DOL Reached Full Feeds to 36 Weeks' PMA Mean (±*SD*)	Zeigler's Theoretical Estimated Growth Velocity Mean (±*SD*)	*p*-value Actual versus Theoretical Estimated
Grams/day	25.34 (5.54)	25.47 (2.25)	$p = 0.885$
Grams/kg/day	14.83 (3.16)	16.07 (2.04)	$p = 0.030$

Table 13. Growth milestones of VLBW infants by Fenton and Lubchenco percentiles

Infant's Growth Milestones-Overall Infants			
Fenton Birth Weight Percentile (All Infants)	**Fenton DOL to RTBW Weight Percentile (All Infants)**	**Fenton 36 Weeks' PMA Weight Percentile (All Infants)**	**Lubchenco 36 Weeks' PMA Weight Percentile (All Infants)**
1 (< 3rd percentile)	4 (< 3rd percentile)	6 (< 3rd percentile)	---
8 (3-10th percentile)	12 (3-10th percentile)	14 (3-10th percentile)	13 (< 10th percentile)
19 (10-50th percentile)	24 (10-50th percentile)	17 (10-50th percentile)	9 (10-25th percentile)
12 (50-90th percentile)	0 (50-90th percentile)	1 (50-90th percentile)	13 (25-50th percentile)
0 (90-97th percentile)	0 (90-97th percentile)	0 (90-97th percentile)	3 (50-75th percentile)
0 (< 36 weeks)	0 (< 36 weeks)	2 (< 36 weeks)*	2 (< 36 weeks)*
Total = 40	Total = 40	Total = 40	Total = 40

Infant's Growth Milestones-AGA Infants			
Fenton Birth Weight Percentile (AGA)	**Fenton DOL to RTBW Weight Percentile (AGA)**	**Fenton 36 Weeks' PMA Weight Percentile (AGA)**	**Lubchenco 36 Weeks' PMA Weight Percentile (AGA)**
0 (< 3rd percentile)	0 (< 3rd percentile)	2 (< 3rd percentile)	---
0 (3-10th percentile)	6 (3-10th percentile)	9 (3-10th percentile)	6 (< 10th percentile)
18 (10-50th percentile)	24 (10-50th percentile)	16 (10-50th percentile)	7 (10-25th percentile)
12 (50-90th percentile)	0 (50-90th percentile)	1 (50-90th percentile)	12 (25-50th percentile)
0 (90-97th percentile)	0 (90-97th percentile)	0 (90-97th percentile)	3 (50-75th percentile)
0 (< 36 weeks)	0 (< 36 weeks)	2 (< 36 weeks)*	2 (< 36 weeks)*
Total = 30	Total = 30	Total = 30	Total = 30

*2 infants did not reach 36 weeks postmenstrual age; 1 died at DOL 31 and 1 was 33 weeks PMA at the end of the study.

Table 13 (continued). Growth milestones of VLBW infants by Fenton and Lubchenco percentiles

Infant's Growth Milestones-SGA Infants			
Fenton Birth Weight Percentile (SGA)	**Fenton DOL to RTBW Weight Percentile (SGA)**	**Fenton 36 Weeks' PMA Weight Percentile (SGA)**	**Lubchenco 36 Weeks' PMA Weight Percentile (SGA)**
1 (< 3rd percentile)	4 (< 3rd percentile)	4 (< 3rd percentile)	---
8 (3-10th percentile)	6 (3-10th percentile)	5 (3-10th percentile)	7 (< 10th percentile)
1 (10-50th percentile)	0 (10-50th percentile)	1 (10-50th percentile)	2 (10-25th percentile)
0 (50-90th percentile)	0 (50-90th percentile)	0 (50-90th percentile)	1 (25-50th percentile)
0 (90-97th percentile)	0 (90-97th percentile)	0 (90-97th percentile)	0 (50-75th percentile)
0 (< 36 weeks)	0 (< 36 weeks)	0 (< 36 weeks)	0 (< 36 weeks)
Total = 10	Total = 10	Total = 10	Total = 10

CHAPTER 5: DISCUSSION

1. Primary Aim - Early Nutrition

This study of the medical nutritional practices in three tertiary care NICUs during the first two weeks of life clearly documented significant differences between both prescribed/intended (P/I) and actual/delivered (A/D) energy and protein intakes administered to VLBW infants and the theoretical estimated nutrient requirements (Ziegler's guidelines). The greatest deficits in A/D energy and protein intakes were during the first week of life with an average of 69% (~ 65 kcal/kg/day) and 89% (~ 3.1 g/kg/day) of the theoretical estimates for energy and protein, respectively. A number of barriers and/or inconsistencies in P/I intakes resulted in a deviation from the theoretical estimated energy and protein requirements; the A/D energy and protein intakes were approximately 15% lower than the P/I intakes. During the second week of life, the A/D energy and protein improved dramatically to an average of 90% (85 kcal/kg/day) and 102% (3.5 g/kg/day) although the differences between the P/I and A/D remained approximately 15%.

Early nutrition during the first two weeks of life is critical in the management of VLBW infants. Some of the goals of the medical nutritional care of these tiny, vulnerable preterm infants are to safely support appropriate growth, (i.e., proportional weight, length and head circumference gains), shorten length of hospital stay and facilitate positive long-term outcomes (neurodevelopmental, etc.). Stephens and associates (2009) (14) recently reported in ELBW infants that, during the first week of life, every 10 kcal/kg/day and each 1 g/kg/day of protein increase were associated with a 4.6 point and 8.2 point increase, respectively in the Mental Development Index at 18 months corrected age. In Stephens and associates' study (14), higher protein intakes also were associated with a lower likelihood of lengths < 10^{th} percentile. The energy intake during the first week in Stephens' study (14) averaged 60 kcal/kg/day, slightly lower than the average energy

intake of 65 kcal/kg/day in our study. In our study, an average increase of ~ 30 kcal/kg/day and ~ 0.5 g/kg/day protein to meet the theoretical estimated nutrient requirements (~ 94 kcal/kg/day and 3.5 g/kg/day protein from PN) could have significantly impacted not only mental development but also the growth of our infants.

The rich supply of nutrients, primarily amino acids that support the growth and development of the fetus is interrupted when an infant is born prematurely. It is widely agreed that the nutrients should be restored as soon as possible in amounts that allow the premature infant to grow similar to the fetus in rates of gain and body composition (51). The rate-limiting nutrient for lean body mass accretion in rapidly growing VLBW infants is protein. The A/D protein intakes are often unknown in routine clinical care since protein intakes are not easily monitored in vulnerable, VLBW infants. In our study, the A/D protein intakes during the first week were surprisingly high (average 3.1 g/kg/day) even though they did not meet theoretical estimates (3.5 g/kg/day). Although earlier studies differ in the summary measures of nutrients, the infants in our study appeared to receive more protein during the first two weeks of life. In a study (Olsen 2002) (58) of infants < 30 weeks GA in 6 NICUs, the mean protein intake was 0.6 g/kg/day on day 3 and only 2.1 g/kg/day on day 7. In another study (Embelton and Cook, 2001) (4), infants ≤ 30 weeks GA received < 2 g/kg/day on day 7. Finally, Stephens et al. (14) reported a first week average protein intake of 1.8 g/kg/day and second week average protein intake of 3.3 g/kg/day for 148 infants < 1000 g (~ 28 weeks GA). More recently, Radmacher et al. (2009) (63) reported intakes of 3.0 g/kg/day and 56 kcal/kg/day administered to ELBW infants in 2006 - 2007.

Increased protein delivery during the first two weeks of life increases weight gain, probably lean body mass and prevents a cumulative protein deficit in infants < 31 weeks GA. Preterm infants typically received intravenous dextrose solutions and energy immediately after birth, followed by increasing parenteral amino acid intakes. There is a

wide range in practices concerning starting and/or advancing PN, the use of intravenous lipid and the introduction of EN. The gradual increases in intakes of protein and energy result in an inevitable nutrient deficit. Embelton (4) calculated the nutrient deficit to be approximately 18 g/kg of protein by the end of the second week of life, assuming energy requirements to be 120 kcal/kg/day and protein requirements 3 g/kg/day. An additional daily protein intake of 0.3 - 0.4 g/kg/day would be required over an 8 week period to make up for this difference (Figure 4). If the actual requirements for protein are higher, i.e., closer to Ziegler's estimated protein requirements, the deficit is even greater.

Protein is overwhelmingly the limiting nutrient for lean body mass accretion; however, adequate energy needs to be provided to spare the protein. It is very difficult to estimate energy requirements during the first few weeks of life in these critically ill VLBW infants. Micheli et al. (1992) (64) established that energy needs for growth of lean body mass are no more than 90 - 100 kcal/kg/day in an elegant analysis of empirical studies. Energy intakes above this presumably are no longer limiting for growth of lean body mass. Kashyap and Heird (1994) (65) concluded that weight gain increases by 3.44 g/kg/day with each additional gram per kg protein. Olson (58) concluded that adding 1 g/kg/day protein to the mean intake in their infants < 30 weeks GA increased growth by 4.1 g/kg/day. When infants are admitted to our NICU, stock amino acid solutions that contain 3.0 g/kg/day protein and 7.5% dextrose are administered until individualized PN begins. This bypasses some of the issues with lower protein intakes during the first week of life; however, A/D energy intakes averaged only 65 kcal/kg/day during the first weeks, substantially less that Ziegler's estimated energy requirements (89 - 101 kcal/kg/day) and the 90 to 100 kcal/kg/day necessary to support lean body mass accretion.

A number of barriers and/or inconsistencies in prescribed/intended intakes resulted in deviations from the theoretical estimated energy and protein requirements. Additionally, VLBW infants have gut immaturity with decreased motility and GI enzyme deficiencies and most VLBW infants have delayed EN secondary to respiratory disease, patent ductus arteriosus, and indomethacin treatment. Many of the smallest infants, especially the ELBW infants have potential for fluid and electrolyte imbalance due to increased surface area/body weight, thin skin and impaired renal function. During the first weeks, procedures such as blood transfusions and peripheral venous catheter access problems also potentially interfere with the continuous delivery of EN and PN.

2. Secondary Aims - Growth Milestones and Outcomes at 36 Weeks' PMA

The VLBW infants in this study averaged a return to birth weight at 10 days of life, with the SGA infants returning to birth weight significantly earlier than the AGA infants, an average of 7 days compared to 11 days of life, respectively. The VLBW infants studied in the early 2000s averaged a return to birth weight between 13 and 17 days of life (Ehrenkranz et al. (31)). In this study, the protein intakes were substantially higher during the first two weeks of life than those seen in studies in the early 2000s. More recently, Radmacher et al. (2009) (63) reported protein intakes in the first week of life of 3.0 g/kg/day and earlier return to birth weight (mean 8.3 ±5 days). In this study, the return to birth weight was not significantly related to the actual/delivered energy and protein intakes during the first week, however, the DOL to reach full EN was significantly related to the first week energy intakes and the birth weight. The higher the energy intakes during the first week, the faster the VLBW infants reached full EN. Interestingly, the smaller infants at birth also reached full EN faster, possibly because of less diuresis (fluid shifts) than more mature infants. In a classic, older study (Berseth 1992) (42), VLBW infants who reached full EN sooner had shorter hospital stays.

It is of significant concern that the VLBW infants in this study averaged 26 days (median 23 days) to reach full EN and that thirteen of these reached full EN at 30 days or later. Many potential factors may explain the delayed EN such as abdominal distention, residuals that are dark green or bilious, apnea and bradycardia, clinical instability/temperature instability, and bloody stools. If any of these events are present, the infants have extended delays in feedings for X-rays and potentially further evaluation for necrotizing entercolitis, sepsis or ileus. While these interruptions may occur, Hanson et al. (62) demonstrated in 81 VLBW infants that a feeding intolerance decision tree significantly improved outcomes. The decision tree provided a safe and objective evaluation to minimize unnecessary interruptions of enteral nutrition without overlooking infants who may be ill. Bloom et al. (27) in 401 VLBW infants also documented the benefits from meaningful evaluation of the processes used in clinical sites to improve clinical outcomes and weight gain in the first 28 days.

Interestingly, when the VLBW infants in this study reached full EN defined as100 kcal/kg/day EN, the growth velocity (15 ±3 g/kg/day) still was significantly lower (6.7%) than Ziegler's theoretical estimated fetal growth velocity (16 ±2 g/kg/day). Although 1 g/kg/day may not seem clinically significant, cumulatively over 7 weeks this becomes a significant amount of weight not gained i.e., about 56 g weight that was not gained by 36 weeks' PMA. In a more recent report of 1187 ELBW infants, Martin et al. (2009) (61) documented that growth velocities of 20 to 30 g/kg/day were associated with ELBW infants maintaining or exceeding their birth weight z-scores.

Growth outcomes at 36 weeks' PMA in this study were significantly better than earlier reports in the 2000s. In this study, EUGR defined as < 10^{th} percentile at 36 weeks' PMA, occurred in 53% of the VLBW infants on the Fenton grid or 34% of the VLBW infants on the Lubchenco grid. A classic National Institute of Child Health and Human Development (NICHD) Neonatal Network study reported in 2001 (33) that 99%

of the infants < 500 g and 97% < 1000 g had extrauterine growth restriction or failure to thrive (< 10th percentile at 36 weeks' PMA). In this study, better growth outcomes compared to prior years may be related to earlier and higher amino acid intakes during the first week of life (3 g/kg/day on DOL 3, 3.6 g/kg/day on DOL 6). Poindexter et al. (2006) (25), in a secondary analysis of 1018 ELBW infants, reported that early amino acids (> 3 g/kg/day, n = 182) were associated with significantly better growth outcomes (weight, length, head circumference) at 36 weeks' PMA than those who received amino acids after 5 days (n = 836).

3. Nutritional Practices

The protocol for nutrition and fluid management may need to be revised to maintain the protein and energy intakes assumed to meet the need of these tiny preterm infants. The nutrition protocol is written to maintain combined EN and PN fluid intakes at 120 mL/kg/day beginning on day of life 8 (Table 14). The prescriptions for PN are written so that 100 mL/kg/day provides the energy and protein assumed to be necessary for appropriate growth; however, as the EN is increased from 20 mL/kg/day to 80 mL/kg/day, the PN is only delivered at 60 mL/kg/day rather than the full 100 mL/kg/day to maintain 140 mL/kg/day total fluids. Thus, the PN provides substantially less than the energy and protein intakes assumed (according to the nutrition protocol) to be provided for VLBW infants. The infants only received approximately 85% of what was prescribed.

These data suggest that, although the fluid management protocol is excellent and consistent with currently recommended standards of practice, it does not consistently provide the theoretical estimates for energy and protein intakes for VLBW infants (Ziegler, (15, 52, 53)). Ziegler et al. (15, 52, and 53) determined the energy and protein intakes required to achieve weight gains similar to the fetus and translated this into the required intakes of EN and PN (Table 2). In general, the energy needs from PN are 85 to 90% of those for EN. PN bypasses digestion and absorption and thus all of the

energy is available for metabolism. The recommended intakes of energy intakes from PN for preterm infants (birth weights 500 - 1200 g) range from 89 kcal/kg/day (500 - 700 g) to 101 kcal/kg/day (901 - 1200 g). The recommended intakes of energy intakes from EN range from 105 to 119 kcal/kg/day. In our study, during the first week, VLBW infants received an average intake of only 65 kcal/kg/day primarily from PN: 78 kcal/kg were prescribed. During the second week, a time of transition to EN, the actual energy intake still only averaged 86 kcal/kg/day although 100 kcal/kg/day were prescribed. Many factors may have interfered with the provision of adequate EN and PN; one of these factors may be the emphasis primarily on fluid rather than on the total nutrition, especially protein.

Two studies documented the benefits of medical nutrition practice changes in improving growth velocity (Bloom 2003) (27) and decreasing EUGR (Hanson 2011) (62) in VLBW infants. In Bloom's study (27), medical nutritional 'processes' associated with 'high' growth velocity sites were identified and provided as alternatives to current practices in 51 sites. Over a 9 month period (January 1 through September 30, 2001), thirty nine of the 51 sites improved the growth velocities of their VLBW from 10.4 ±6 g/day to 12.5 ±6 g/day (27). The units implemented the specific recommendations to a variable degree and those that did not had slower rates of gain. These data emphasis the idea, that there must be investment of time and energy to implement nutrition protocols and effective changes in practices. In a more recent study (2011), Hanson et al. (62) implemented a number of medical nutrition practice changes designed to decrease EUGR. In the post implementation phase, EUGR (< 10^{th} percentile for weight at 36 weeks' PMA) decreased from 57% to 28% at discharge.

Table 14. Riley Hospital for Children at IU Health feeding protocol for infants with birth weight < 1250 g

Day of Life	PN mL/kg/d	MIV fluid mL/kg/d	Enteral feeds mL/kg/d	Total fluids mL/kg/d
0	60	20-40		80-100
1	75	5-25		80-100
2	75	5-25		80-100
3	100	D/C	20	120
4	100		20	120
5	100		20	120
6	100		20	120
7	100		20	120
8	100		40	140
9	80		60	140
10	60		80	140
11	40		100	140
12	D/C		120	120
13			140	150-180
14			160	150-180
15			180	150-180

Abbreviations: D/C = discontinue PN; MIV = med-intravenous fluid.

4. Strengths and Weaknesses

This study makes a substantial contribution to the science of nutrition and the early nutrition, feeding and growth of VLBW infants. The strengths of the study include the fact that data were prospectively and meticulously obtained daily by trained personnel with an electronic computerized tool that stored data without identifiers. Another strength was that a validated and accurate nutrition electronic assessment tool was used to monitor and accurately calculate the P/I and A/D energy and protein intakes.

A weakness relates to the fact that the numbers of infants in each of the GA, weight and SGA/AGA categories were too small to complete evaluation of potential effects of early nutrition, growth milestones and growth outcomes on these subgroups. This study needs to be extended to other NICUs within the country. This would allow documentation of a variety of clinical practices and feeding protocols and their subsequent outcomes. Although the primary aim was to determine the provision of energy and protein during the first two weeks, the analyses of reasons for the barriers and inconsistencies in nutrition delivery would be very informative and provide specific rational for the development of nutritional protocols and interventions that will overcome specific obstacles/barriers.

The ultimate benefit from studies such as these is that the improvement in quality outcomes of the lives of VLBW infants, i.e., potentially improved neurodevelopmental and other functional outcomes, earlier maturation of organ systems, shortened lengths of stay in the hospital and potentially decreased medical expenses. A classic outcomes study and/or translational study is needed to document the benefits and any potential risks from closer attention and monitoring of nutritional care and clinical practice during the first weeks of life in a level III NICU. The infants in this study were unable to achieve the theoretical estimated energy and protein requirements in the first week of life and did

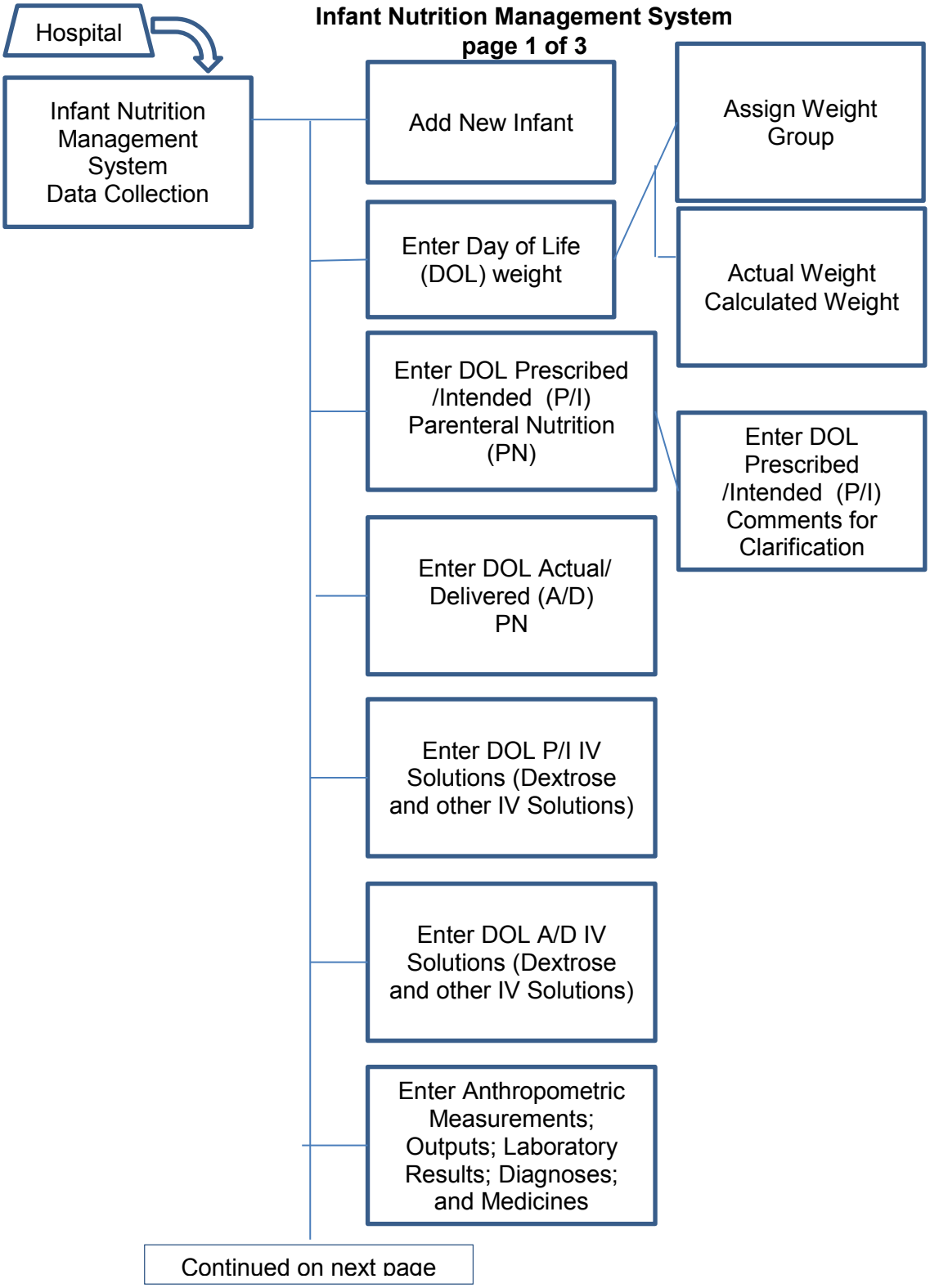
not achieve the theoretical estimated fetal growth velocities. Studies of medical nutritional practices and point of care strategies for tracking and trending nutritional data are needed to safely support improved early nutrition, growth velocities and growth outcomes at 36 weeks' PMA.

5. Summary

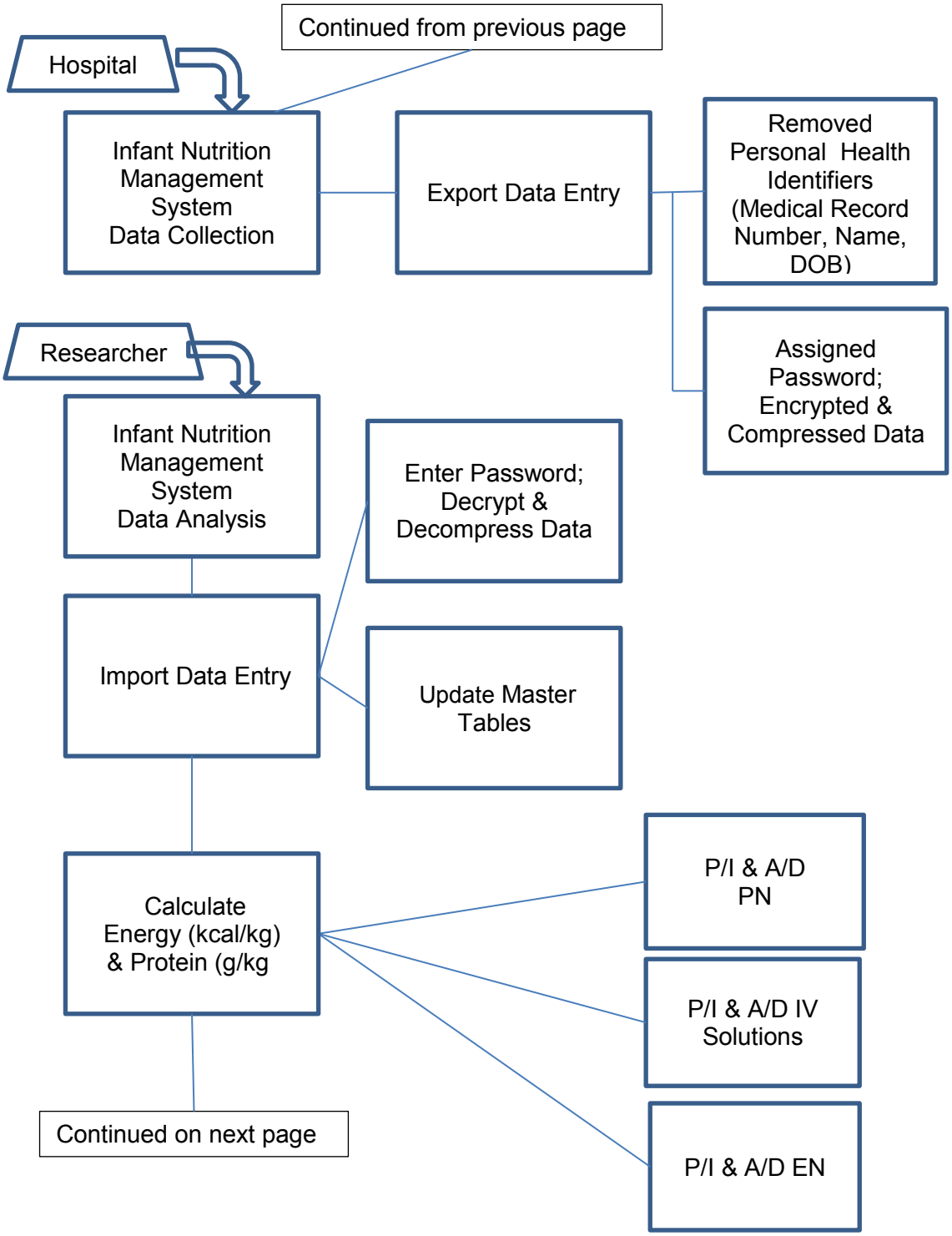
Medical nutritional practices in three tertiary care NICUs during the first two weeks of life clearly documented significant differences between both prescribed/intended (P/I) and actual/delivered (A/I) energy and protein intakes administered to VLBW infants and the theoretical estimated nutrient requirements (Ziegler's guidelines) (19, 26). During the first week of life, the percentages of P/I and A/D energy (mean 65 kcal/kg/day) and protein (mean 3.1 g/kg/day) were significantly less than theoretical estimated requirements and A/D intakes were ~ 15% less than P/I due to numerous interruptions and medical nutritional complications in these critically ill, tiny babies. During the second week, the A/D intakes of energy (mean 86 kcal/kg/day) and protein (3.5 g/kg/day) improved although the differences P/I and A/D were consistently 15%. The energy but not protein intakes during the first week were significantly related to time to reach full EN (defined as 100 kcal/kg/day). The average growth velocity (mean 15 g/kg/day) was significantly less than the theoretical estimated fetal growth velocity (mean16 g/kg/day) from time to reach full EN to 36 weeks' PMA. At 36 weeks' PMA, 53% of the VLBW infants had EUGR defined as < 10^{th} percentile on the Fenton premature infant grid and 34% had EUGR on the Lubchenco premature infant grid. Relative to earlier data, the growth outcomes at 36 weeks' PMA were surprisingly improved; however, one third to one half the infants were still failing to thrive at 36 weeks' PMA. Significant concerns remain regarding the infants who have EUGR because of the association of inadequate early nutrition to growth (including head circumference) and cognitive development at 18 months of age.

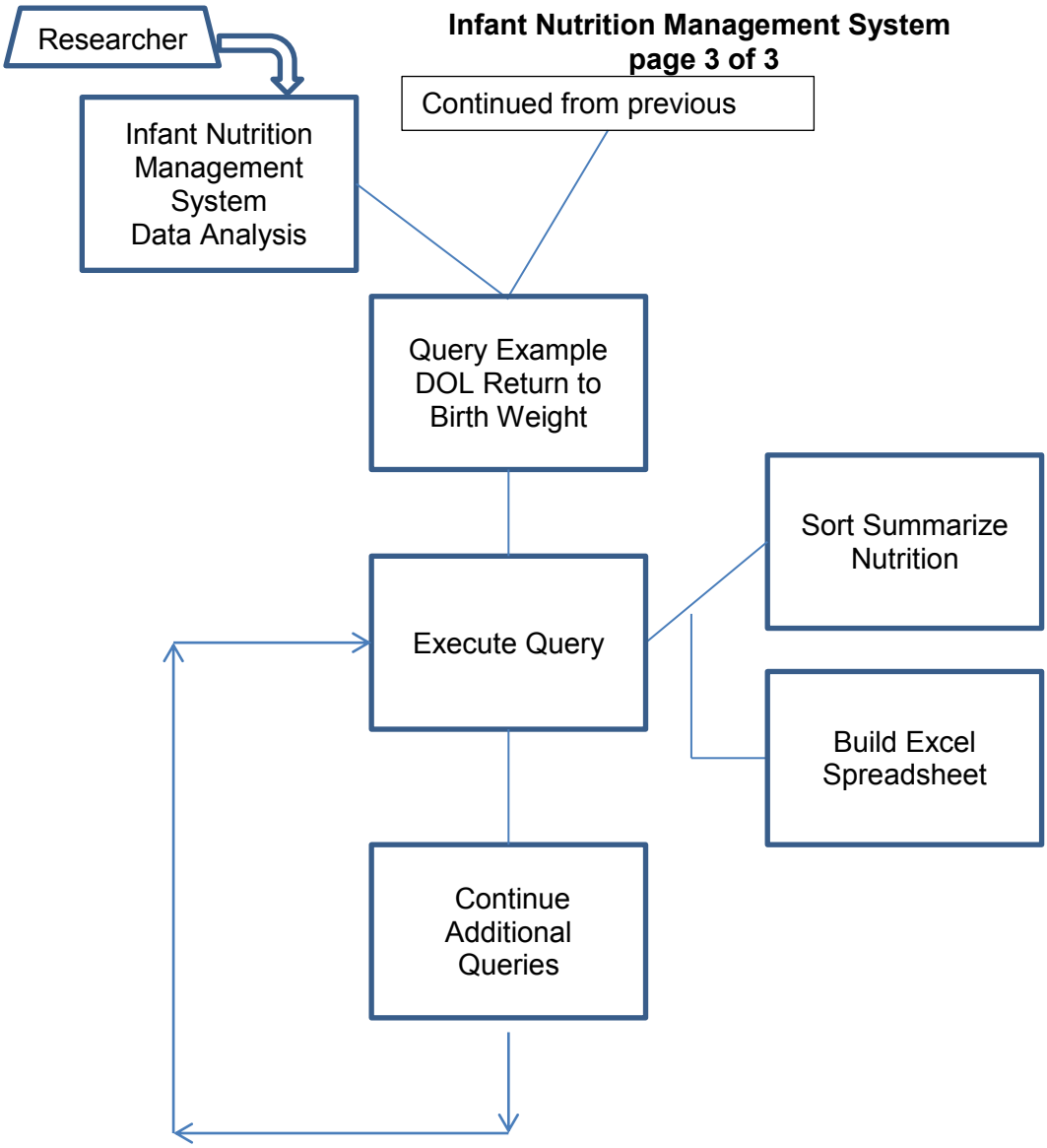
APPENDIX A

A flow chart of inputs and outputs of the computerized system


Hospital
Infant Nutrition Management System Data Collection
Infant Nutrition Management System
page 1 of 3
Add New Infant
Assign Weight Group
Enter Day of Life (DOL) weight
Actual Weight
Calculated Weight
Enter DOL Prescribed /Intended (P/I) Parenteral Nutrition (PN)
Enter DOL Prescribed /Intended (P/I) Comments for Clarification
Enter DOL Actual/ Delivered (A/D) PN
Enter DOL P/I IV Solutions (Dextrose and other IV Solutions)
Enter DOL A/D IV Solutions (Dextrose and other IV Solutions)
Enter Anthropometric Measurements; Outputs; Laboratory Results; Diagnoses; and Medicines
Continued on next page

Infant Nutrition Management System
page 2 of 3




Researcher
Infant Nutrition Management System page 3 of 3
Continued from previous
Infant Nutrition Management System Data Analysis
Query Example DOL Return to Birth Weight
Sort Summarize Nutrition
Execute Query
Build Excel Spreadsheet
Continue Additional Queries

APPENDIX B

Internal Review Board (IRB) Notice of Expedited Approval and Notice of Expedited Approval - Amendment

INDIANA UNIVERSITY

OFFICE OF RESEARCH ADMINISTRATION

To: BRENDA BRADLEY PEDIATRICS
PED-NEONATAL MEDICINE

From: IU Human Subjects Office
Office of Research Administration – Indiana University

Date: July 19, 2011

RE: NOTICE OF EXPEDITED APPROVAL

Protocol Title: Comparing Actual vs. Prescribed Energy and Protein Intakes for Extremely Low Birth Weight (ELBW) Infants: An Observational Pilot Study

Protocol #: 1106005804

Funding Agency/Sponsor: None

IRB: IRB-05, IRB00004961

Exclusion Date: July 14, 2012

The above-referenced protocol was reviewed by the Institutional Review Board (IRB-05). The protocol meets the requirements for expedited review pursuant to §46.110, Category (5) . The protocol is approved for a period of July 15, 2011 through July 14, 2012. This approval does not replace any departmental or other approvals that may be required.

If you submitted and/or are required to provide participants with an informed consent document, study information sheet, or other documentation, a copy of the enclosed approved stamped document is enclosed and must be used.

As the principal investigator (or faculty sponsor in the case of a student protocol) of this study, you assume the following responsibilities:

1. **CONTINUING REVIEW:** Federal regulations require that all research be reviewed at least annually. You may receive a "Continuation Renewal Reminder" approximately two months prior to the expiration date; however, it is the Principal Investigator's responsibility to obtain review and continued approval before the expiration date. If continued approval is not received by the expiration date, the study will automatically expire, requiring all research activities, including enrollment of new subjects, interaction and intervention with current participants, and analysis of identified data to cease.

2. **AMENDMENTS:** Any proposed changes to the research study must be reported to the IRB prior to implementation. Only after approval has been granted by the IRB can these changes be implemented. An amendment form can be obtained at: http://researchadmin.iu.edu/HumanSubjects/hs_forms.html.

3. **UNANTICIPATED PROBLEMS AND NONCOMPLIANCE:** Unanticipated problems and noncompliance must reported to the IRB according to the policy described in the Unanticipated Problems and Noncompliance SOP, which can be found at http://researchadmin.iu.edu/HumanSubjects/hs_policies.html. NOTE: If the study involves gene therapy and an event occurs which requires prompt reporting to the IRB, it must also be reported to the Institutional Biosafety Committee (IBC).

4. **UPDATED INVESTIGATIONAL REQUIREMENTS:** For investigational drug or device studies, updated clinical investigational brochures must be submitted as they occur. These are submitted with an amendment form.

5. **ADVERTISEMENTS:** Only IRB-approved advertisements may be used to recruit participants for the study. If you submitted an advertisement with your study submission, an approved stamped copy is provided with the approval. To request approval of an advertisement in the future, please submit an amendment, explaining the mode of communication and information to be contained in the advertisement.

6. **COMPLETION:** Prompt notification must be made to the IRB when the study is completed (i.e. there is no further subject enrollment, no further interaction or intervention with current participants, including follow-up, and no further analysis of identified data). To notify the IRB of study closure, please obtain a close-out form at http://researchadmin.iu.edu/HumanSubjects/hs_forms.html.

7. **LEAVING THE INSTITUTION:** The IRB must be notified of the disposition of the study when the principal investigator (or faculty sponsor in the case of a student project) leaves the institution.

3. **VULNERABLE POPULATION:** Please note that there are special requirements for the inclusion of prisoners in research. You may not enroll or otherwise include an individual who is or becomes a prisoner while enrolled in the research. For additional information on the requirements for including prisoners in research, please refer to http://researchadmin.iu.edu/HumanSubjects/hs_policies.html.

Note: SOPs exist covering a variety of topics that may be relevant to the conduct of your research. For more information on the relevant policies and procedures, go to http://researchadmin.iu.edu/HumanSubjects/hs_policies.html.

You should retain a copy of this letter and any associated approved study documents (e.g. informed consent or information sheet) for your records. Please refer to the project title and number in future correspondence with our office. Additional information is available on our website at http://researchadmin.iu.edu/HumanSubjects/index.html. Please contact our office if you have questions or need further assistance.

Thank you.

INDIANA UNIVERSITY INSTITUTIONAL REVIEW BOARD (IRB)

HIPAA & RECRUITMENT CHECKLIST

IRB STUDY NUMBER: 1106005804
PRINCIPAL INVESTIGATOR: Brenda Poindexter, MD, MS
DOCUMENT DATE: 5/30/2011

You must complete this checklist **if you are a Covered Entity or you are involving a covered entity in your research AND protected health information (PHI) will be utilized, accessed, collected, or generated as part of the study**. Federal privacy regulations impact how you may use an individual's health information to identify, recruit and contact potential research subjects. Under the Health Insurance Portability and Accountability Act (HIPAA) recruitment is considered research and requires either an authorization or a waiver of authorization.

While an authorization or waiver of authorization may not always be required by HIPAA, Indiana University policy requires that the subject be contacted by someone the patient would recognize as being involved in their care.

Please type only in the gray boxes. To mark a box as checked, double-click the box, select "checked", and click "OK".

Section I: Recruitment Strategies

Please describe how you will handle recruitment for your study:

1. Describe how potential subjects will be initially identified (include specific source, e.g. databases, medical records, advertisements, newsletters, self-referral, physician referral, from clinics, etc.):

   Infants with birth weights ≤ 1000 grams will be included using information from existing medical records.

2. Describe how potential subjects who are identified will be contacted (e.g. letter, phone call, face-to-face) and who will be contacting them (e.g. their physician, research coordinator, nurse, etc.). Include a copy of all information to be shared with or intended to be seen by potential subjects.

   Registered dietitian will collect infant's nutritional data and growth outcomes. Observational pilot data only study.

3. Is the investigator currently conducting competing studies? Competing studies refers to two or more studies which utilize overlapping or very similar eligibility criteria.
   ☒ No.
   ☐ Yes. Please describe the plan to ensure fair and unbiased recruitment:

   NOTE: Allowing the Principal Investigator or the subject to choose one study over another is rarely acceptable. Consider randomization procedures or exclusive enrollment in one study at a time.

Please check <u>all</u> the recruitment strategies below that will be utilized.

Please be aware that recruitment includes identification, review of records to determine eligibility or any contact to determine a potential subject's interest in a study.

☒ 1. **<u>Care Provider</u>:** Recruitment will be done by the researcher who is a physician, dentist, nurse or other licensed independent practitioner who has provided care for the patient.

Neither an Authorization from the Subject nor approval to Waive Authorization from the IRB is required.

☐ 2. **<u>Authorized Delegate – Same Organization</u>:** Recruitment will be done by a researcher who did not provide care for the patient, but who will act as an authorized delegate of the treatment provider and who is part of the same Department or practice plan. (In the case of the Departments of Pediatrics, Surgery and Medicine, this will be limited to providers within the same Division.) This may include the researcher's coordinator as long as the Research Coordinator is part of the same Division, Department or Practice Plan as the PI or co-investigator.

The researcher must obtain approval from the treatment provider to act as a representative contacting the potential subject. For example: "I am a colleague of Dr. "X", or I work for Dr. X who gave me permission to contact you regarding…." However, the IRB will judge the appropriateness of this approach on a case-by-case basis.

Neither an Authorization from the Subject nor approval to Waive Authorization from the IRB is required.

☐ 3. **Authorized Delegate – Separate Organization:** If the researcher is not the treatment provider and is not part of the same Division, Department or practice plan of the treatment provider, then contact must be made as follows: (NOTE: This includes Research Coordinators who are not part of the treatment provider's Division, Department or practice plan.). Please check all that apply.

☐ The treatment provider will direct the prospective subject to contact the researcher.

Neither an Authorization from the Subject nor approval to Waive Authorization from the IRB is required.

☐ The treatment provider will obtain an authorization from the potential subject to release the subject's demographic and/or health information to the researcher.

Submit an Authorization for recruitment for IRB Approval.

☐ Neither of the previous options applies to this study. A waiver of authorization will be required, but will only be allowed in limited circumstances where the appropriate justification is provided to the IRB.

Complete the Waiver of Authorization Section on this Checklist.

☐ 4. **Self Referral** – A subject responds to an ad, online listing, or media relations effort for a specific study, or places a cold call regarding research studies in general.

☐ If you need to do a basic initial screening, you may gather minimal information necessary to determine whether the individual is eligible for further screening and/or enrollment. For instance, obtaining the individual's contact information and explaining two or three major inclusion/exclusion criteria would be acceptable. Covering the entire Informed Consent or an exhaustive list of inclusion/exclusion criteria does not constitute a "basic" initial screening.

Neither an Authorization from the Subject nor approval to Waive Authorization from the IRB is required.

☐ If you need to gather additional detail about an individual's health to determine the individual's eligibility, an authorization or waiver of authorization is required. Please note that a telephone script must be submitted unless an authorization will be obtained.

Submit an Authorization for recruitment for IRB Approval or Complete the Waiver of Authorization Section on this Checklist.

☐ If you wish to add an individual's information to an IRB-approved recruitment database for future research, an authorization or waiver of authorization is required. (See database questions below.)

Submit an Authorization for recruitment for IRB Approval or Complete the Waiver of Authorization Section on this Checklist.

☐ If you wish to refer the individual to another research area/department, you must give the potential subject the researcher's contact information*:

Neither an Authorization from the Subject nor approval to Waive Authorization from the IRB is required.

☐ Recruitment practices that were approved prior to April 14, 2003, which do not fall into any of the above listed categories.

Complete the Waiver of Authorization Section on this Checklist.

** This does not prohibit or interfere with the ability to refer patients for treatment purposes to other providers.*

Section II: Recruitment Databases

Instructions: This section applies to databases that are developed and/or used exclusively for research or recruitment purposes and not for patient care. Select from the Recruitment Strategies ABOVE for recruitment strategies involving clinical databases (e.g. physician patient databases, CareWeb, Regenstrief, etc.).

☐ 1. A recruitment database that includes health or demographic information will be developed and used to identify and recruit potential research subjects. NOTE: If you plan to use this research database as a recruitment tool for future research projects, then a separate research database protocol should be submitted to the IRB for approval.

Please describe:

☐ 2. An existing IRB-approved recruitment database will be used for this project.

Please Provide the IRB # for the approved Recruitment Database Protocol:

☐ 3. An existing research database (i.e. data that was previously collected for research purposes and not patient care) will be used for recruitment for this project.

Please describe:

Submit an Authorization for recruitment for IRB Approval or request a Waiver of Authorization in Section II below.

SECTION III: AUTHORIZATION FOR THE USE/DISCLOSURE OF PROTECTED HEALTH INFORMATION

☐ I will be obtaining an authorization for the release of health information for research at the time of enrollment/consent. Please submit a copy of the authorization for review.

☒ I am requesting a waiver of authorization for the release of health information for the following procedures (*check all that apply and complete questions 1-3 below*):

- ☐ **Recruitment**. A waiver of authorization for recruitment allows the study team to view potential participants' PHI prior to enrollment in the study in order to determine eligibility, without requiring potential participants to sign a written authorization.
- ☒ **Participation in the study**. A waiver of authorization for participation allows the study team to utilize, access, collect, or generate study subjects' PHI without requiring subjects to sign a written authorization.

NOTE: Approval of a waiver of authorization for *recruitment* does not imply approval of a waiver of authorization for *participation*. Any waiver of authorization, whether for recruitment or participation, requires you to track the disclosures of health information for a period of six years.

Request for a waiver of authorization for the release of health information

1. Explain how this research involves no more than minimal risk of loss of privacy to the subject.

The data collection will be completed by the co-investigator NICU registered dietitian. The patient information will be de-identified. The de-identified information will be stored in an Excel spreadsheet. There will not be hard copies kept. There will be a log with patient's name and corresponding unique assigned ID, kept as a hard copy under lock and key in the dietitian's office in the Newborn Intensive Care Unit (NICU).

a. Describe the plan for protecting the identifiers from improper use and disclosure.

In order to protect the identifiers from improper use and disclosure, they can only be accessed by the co-investigator NICU dietitian who has been authorized to participate in the study. The PHI information will be removed and the remaining information will be stored in an Excel spreadsheet. The patient names and corresponding unique assigned ID will be kept under lock and key in the dietitian's office.

b. Describe the plan to destroy the identifiers at the earliest opportunity that is appropriate for the research study. Identifiers may only be maintained following completion of a study if there is a legitimate reason for maintaining the data (e.g required by law, etc.).

The file folders containing PHI information will be erased at the end of the study. This will be accomplished by a hard drive utility program (Acronis True Image's File Shredder) which guarantees the complete destruction of files through its use of a military security algorithm.

c. Provide written assurances that the identifiable health information will not be re-used or disclosed to any other person or entity, except as required by law, for authorized oversight of the project or for other permitted research purposes.

I understand that the identifiable PHI is not be re-used or disclosed to any other person or entity, except as required by law, for authorized oversight of the project or for other permitted research purposes.

2. Explain how the research could not be practicably conducted without waiver of authorization or an alteration to the authorization form.

This is an observational pilot study where this study is trying to obtain generalized data about nutritional intake during the first couple weeks for infants less than 1000 grams. In order to obtain this generalized data (which is a precondition for implementing "best practices" and optimizing recommended standards), it is necessary to ensure that all populations are equally represented and to not have the data biased in any way. Loss of even a few infants could significantly introduce a bias to this data.

3. Explain how the research could not be practicably conducted without access to and use of the individually identifiable health information.

This research requires the observation of an infant's parenteral & enteral nutrition intake and growth velocity. This information is located in the patient's medical records. Infant's PHI is used as keys to access these records. Therefore, it is impossible to acquire this data without each infant's PHI.

NOTE: If the IRB approves a waiver of authorization, the PI is responsible for tracking all disclosures of health information for a period of six years. For additional information, please see the Confidentiality and Privacy SOP.

IRB Approval of Waiver of Authorization:

Signature:_____ Date Approved: 6 July 2011

INDIANA UNIVERSITY

OFFICE OF RESEARCH ADMINISTRATION

To: BRENDA BRADLEY PHINDEXTER
PED-NEONATAL MEDICINE

From: IU Human Subjects Office
Office of Research Administration – Indiana University

Date: February 21, 2012

RE: NOTICE OF EXPEDITED APPROVAL - AMENDMENT

Protocol Title: Comparing Actual vs. Prescribed Energy and Protein Intakes for Extremely Low Birth Weight (ELBW) Infants: An Observational Pilot Study

Protocol #: 1106005004

Funding Agency/Sponsor: None

IRB: IRB-05, IRB00004961

Expiration Date: July 14, 2012

An amendment to your above-referenced protocol was approved by the Institutional Review Board on February 10, 2012. The protocol meets the requirements for expedited review pursuant to §46.110(b)(2). The changes described in the amendment can now be implemented, unless any departmental or other approvals are required.

If you submitted a revised informed consent document a copy of the approved stamped document is enclosed and must now be used.

You should retain a copy of this letter and any associated approved study documents for your records. All documentation related to this protocol must be maintained in your files for audit purposes for at least three years after closure of the research; however, please note that research studies subject to HIPAA may have different requirements regarding file storage after closure. Additional information is available on our website at http://researchadmin.iu.edu/HumanSubjects/index.html. If you have any questions, please contact our office at the below address.

Thank you.

INDIANA UNIVERSITY INSTITUTIONAL REVIEW BOARD (IRB)

STUDY AMENDMENT

Reviewing IRB (please choose one):
Biomedical: ☐ IRB-02 ☐ IRB-03 ☐ IRB-04 ☒ IRB-05
Behavioral: ☐ IRB-01 ☐ IUB IRB

IRB STUDY NUMBER: 1106005804
AMENDMENT NUMBER: (Item 002-A001) 1

Please type only in the gray boxes. To mark a box as checked, double-click the box, select "checked", and click "OK".

SECTION I: INVESTIGATOR INFORMATION

Principal Investigator:
Name *(Last, First, Middle Initial)*: **Poindexter, Brenda MD, MS**
Department: Pediatrics Phone: 317-274-4768 E-Mail: bpoindexe@iupui.edu

Additional Study Contact:
Name: Student Contact ,Debbie Abel Phone: 317-201-4528 E-Mail: dmabel@iupui.edu

Project Title: **Comparing Actual vs. Prescribed Energy and Protein Intakes for Extremely Low Birth Weight (ELBW) Infants: A n Observational Pilot Study**
Sponsor/Funding Agency: N/A Sponsor Number. _____
Sponsor Amendment Number. _____

SECTION II: STUDY INFORMATION

This study is:
☒ Open to enrollment
☐ Closed to enrollment

Number of active subjects: 16

SECTION III: AMENDMENT DESCRIPTION

1. Provide a complete description of the proposed change(s) included in this amendment:
   Inclusion was changed to ELBW infants ≤ 30 weeks gestational age at birth instead of ≤ 1000grams

2. State the justification/rationale for this amendment. If risks are being updated, please provide specific justification:
   In discussions with our neonatologists we decided that restricting entry to those infants with a birthweight less than 1000 grams has left out certain ELBW infants who need the same issues addressed to improve their care.

3. Is the study sponsored?
   ☒ No.
   ☐ Yes. Check the appropriate line below and provide with this amendment, as applicable:
   - ☐ A copy of the sponsor's amendment, if the amendment came from the sponsor.
   - ☐ A copy of your notice to the sponsor of this change, if you initiated the amendment.
   - ☐ A copy of the approved amendment will be sent to the sponsor.
   - ☐ None of the above apply. Please explain: _____

4. Do the proposed change(s) described in this amendment alter the risk to benefit assessment?
   ☒ No.
   ☐ Yes. Please describe how the assessment is altered: _____

5. Do the proposed change(s) described in this amendment require changes to the informed consent and/or assent document(s) or process?
   ☒ N/A. Informed consent, written documentation of informed consent, and/or assent has been waived for this study. Skip to item 6 below.
   ☐ No. Skip to item 6 below.
   ☐ Yes. Answer items A and B below.

A. Check the appropriate line below.
- ☐ The new informed consent and/or assent document(s) are in addition to the current one(s).
- ☐ The new informed consent and/or assent document(s) replace the current one(s).
  If there are multiple consent and/or documents for this study, please indicate which consent and/or assent document(s) are to be replaced. _____
- ☐ N/A. Changes are being made to the informed consent process only and informed consent document(s) will not change.

B. Will enrolled subjects be informed of the change(s) described in this amendment?
- ☐ No. Please explain why not: _____
- ☐ Yes. Will enrolled subjects be re-consented and/or re-assented?
  - ☐ Yes.
  - ☐ No. Please explain how enrolled subjects will be notified: _____

6. Amendment includes:

- ☐ Assent, dated: _____
  Number of assent documents: _____
- ☐ Authorization, dated: _____
  Number of authorizations: _____
- ☐ Clinical Investigator's Brochure, dated: _____
- ☐ Expedited Research Checklist, dated: _____
- ☐ Exempt Research Checklist, dated: _____
- ☐ HIPAA & Recruitment Checklist, dated: _____
- ☐ Informed Consent, dated: _____
  Number of consent documents: _____
- ☐ Investigator List, dated: _____
- ☒ Protocol, dated: 1/11/12
- ☐ Recruitment materials (please list and date): _____
- ☐ Request form(s) for vulnerable population(s) (please list and date); _____
- ☐ Surveys, questionnaires (please list and date): _____
- ☒ Summary Safeguard Statement or HUD Form, dated: 1/11/12
- ☐ Study Information Sheet
- ☐ Other (please list and date): _____

NOTE: Only documents that are being changed as a result of the amendment should be attached and checked in items 6 above. Listing document dates are optional and only necessary if required by the investigator or sponsor.

NOTE TO INVESTIGATORS: Study amendments *may not* be instituted until approval from the IRB is given.

Please indicate the type of amendment you are submitting. Please see the Guidelines for Determining an Amendment Type available on the IU Human Subjects Office website for additional information. **Please note that the IRB makes the final determination with regard to whether or not the amendment is acceptable for expedited review or if it requires review at a convened IRB meeting.**

☒ **Minor Amendment.** Change(s) do not significantly affect the safety of subjects and is acceptable for expedited review per 45 CFR 46.110(b)(2)/21 CFR 56.110(b)(2).

☐ **Major Amendment.** Changes potentially involve increased risks or discomforts or decrease potential benefit. The amendment requires review at a convened IRB meeting.

SECTION IV: INVESTIGATOR STATEMENT OF COMPLIANCE

By submitting this form, the Principal Investigator assures that all information provided is accurate. He/she assures that procedures performed under this project will be conducted in strict accordance with federal regulations and Indiana University policies and procedures that govern research involving human subjects. He/she acknowledges that he/she has the resources required to conduct research in a way that will protect the rights and welfare of participants, and that he/she will employ sound study design which minimizes risks to subjects. He/she agrees to submit *any* change to the project (e.g. change in principal investigator, research methodology, subject recruitment procedures, etc.) to the Board in the form of an amendment for IRB approval prior to implementation.

SECTION V: IRB APPROVAL

This amendment, including documentation noted above, has been reviewed and approved by the Indiana University IRB as meeting the criteria for IRB approval as outlined in 45 CFR 46.111(a). I agree with the investigator's assessment above regarding whether the amendment is a minor or major amendment, unless otherwise noted.

Authorized IRB Signature: _____ IRB Approval Date: 10/FEB/12

Printed Name of IRB Member: _____

For IU Human Subjects Office use only.

Recorded in the Minutes of: _____

APPENDIX C

Statistical Analysis for the mean energy intakes ±*SD* and minimum - maximum as a percent of theoretical estimates of energy requirements (Ziegler's guidelines) of VLBW infants during the first 14 days of life, week 1, week 2 and both weeks. Percentage was calculated as prescribed/intended (P/I) or actual/delivered (A/D) energy intakes divided by theoretical estimates of energy requirements.

Time Period (Day of Life)	Percent of P/I Energy[1] Mean ±*SD* Min - Max	*p*-value, Percent of P/I Energy	Percent of A/D Energy[1] Mean ±*SD* Min - Max	*p*-value, Percent of A/D Energy
1	57.62 (16.22) 0 - 96.77	< 0.0001*	41.59 (10.31) 16.85 - 85.16	< 0.0001*
2	67.84 (16.64) 0 - 98.22	< 0.0001*	54.58 (14.68) 1.10 - 81.18	< 0.0001*
3	79.20 (18.59) 45.39 - 128.76	< 0.0001*	64.66 (17.91) 24.23 - 107.35	< 0.0001*
4	83.47 (19.30) 40.18 - 113.86	< 0.0001*	69.62 (19.48) 30.57 - 106.63	< 0.0001*
5	91.78 (16.09) 57.53 - 125.90	0.0025	79.82 (14.43) 50.85 - 117.78	< 0.0001*
6	95.20 (17.09) 51.42 - 130.03	0.0834	84.48 (17.62) 49.44 - 114.94	< 0.0001*
7	98.60 (19.98) 60.83 - 138.60	0.6611	88.01 (18.71) 47.93 - 124.66	0.0002*
8	100.69 (19.30) 70.00 - 137.20	0.8229	86.33 (19.51) 32.03 - 125.52	< 0.0001*
9	100.69 (22.20) 58.92 - 148.37	0.8458	88.30 (21.29) 40.98 - 124.61	0.0013*
10	104.16 (21.12) 73.39 - 157.19	0.2208	90.72 (16.48) 56.08 - 120.10	0.0010*
11	107.50 (24.42) 72.89 - 175.67	0.0593	91.47 (19.24) 44.43 - 135.08	0.0078
12	107.77 (29.46) 37.73 - 169.45	0.1033	88.97 (23.25) 24.16 - 130.77	0.0047
13	104.71 (28.87) 51.23 - 183.28	0.3083	92.50 (18.70) 48.91 - 129.40	0.0153
14	112.49 (33.96) 62.24 - 206.01	0.0253	94.09 (20.95) 57.59 - 149.67	0.0821
Week 1 (days 1 - 7)	82.11 (22.40) 0 - 138.60	< 0.0001*	69.23 (22.49) 1.10 - 124.66	< 0.0001*
Week 2 (days 8 - 14)	105.43 (26.10) 37.73 - 206.01	0.0006*	90.34 (19.95) 24.16 - 149.67	< 0.0001*
Overall (days 1 - 14)	93.83 (26.96) 0 - 206.01	< 0.0001*	79.86 (23.71) 1.10 - 149.67	< 0.0001*

[1] Percent of prescribed and actual values were calculated compared to Ziegler's theoretical estimated energy requirements.

* Indicates a significant difference at a Bonferroni adjusted alpha level of 0.05 (adjusted *p*-value = 0.0015), for a one-sided t-test, with a null hypothesis that the percentage is 100.

APPENDIX D

Statistical Analysis for the mean energy intakes ±*SD* and minimum - maximum as kcal/kg/day compared to theoretical estimates of energy requirements (Ziegler's guidelines) of VLBW infants during the first 14 days of life, week 1, week 2 and both weeks. Differences in energy intakes were calculated as theoretical estimates minus prescribed/intended (P/I) or actual/delivered (A/D) energy intakes.

Time Period (Day of Life)	Theoretical Estimated Energy Minus P/I Energy[1] Mean ±*SD* Min - Max	*p*-value, Theoretical Estimated Energy Minus P/I	Theoretical Estimated Energy Minus A/D Energy[1] Mean ±*SD* Min - Max	*p*-value, Theoretical Estimated Energy Minus A/D
1	39.7 (15.1) 3.3 - 89.0	< 0.0001*	55 (10.6) 15.0 - 84.0	< 0.0001*
2	29.9 (14.9) 1.8 - 89.0	< 0.0001*	42.4 (13.0) 19.0 - 88.0	< 0.0001*
3	19.4 (17.3) -26.5 - 48.6	< 0.0001*	32.8 (16.3) -7.4 - 67.4	< 0.0001*
4	15.5 (17.9) -12.8 - 53.2	< 0.0001*	28.5 (18.4) -5.9 - 63.0	< 0.0001*
5	7.6 (14.8) -23.1 - 37.8	0.0024	18.7 (13.4) -18.0 - 43.8	< 0.0001*
6	4.4 (15.7) -26.7 - 43.2	0.0872	14.4 (16.3) -14.6 - 45.0	< 0.0001*
7	0.9 (18.7) -37.1 - 34.9	0.7556	10.9 (17.4) -24.9 - 46.3	0.0003*
8	-1.0 (18.3) -37.1 - 27.1	0.7204	12.6 (18.5) -23.5 - 68.7	0.0001*
9	-1.1 (21.3) -52.2 - 36.6	0.7501	10.6 (19.7) -24.9 - 52.5	0.0015*
10	-4.2 (20.9) -61.8 - 28.7	0.2120	8.8 (16.0) -20.3 - 46.3	0.0012*
11	-7.4 (24.4) -81.7 - 27.4	0.0613	7.8 (18.2) -32.3 - 49.5	0.0095
12	-7.6 (28.1) -70.1 - 55.4	0.0960	10.4 (21.5) -27.5 - 67.5	0.0040
13	-4.5 (27.5) -76.6 - 43.4	0.3042	7.1 (17.5) 27.1 - 45.5	0.0141
14	-11.9 (32.2) -97.5 - 37.8	0.0247	5.6 (20.1) -45.7 - 42.8	0.0875
Week 1 (days 1 - 7)	16.6 (20.8) -37.1 - 89.0	< 0.0001*	28.7 (21.1) -24.9 - 88.0	< 0.0001*
Week 2 (days 8 - 14)	-5.4 (25.1) -97.5 - 55.4	0.0004*	9.0 (18.8) -45.7 - 68.7	< 0.0001*
Overall (days 1 - 14)	5.6 (25.5) -97.5 - 89.0	< 0.0001*	18.8 (22.2) -45.7 - 88.0	< 0.0001*

[1] Differences were calculated as Ziegler's theoretical estimated energy requirements minus the prescribed or actual energy intakes.

* Indicates a significant difference at a Bonferroni adjusted alpha level of 0.05 (adjusted *p*-value = 0.0015), for a two-sided t-test, with a null hypothesis that the difference is 0.

APPENDIX E

Mean prescribed/intended (P/I) and actual/delivered (A/D) energy (kcal/kg/day) and protein (g/kg/day) intakes for week 1, week 2 and both weeks for VLBW infants by birth weight categories.

Prescribed/Intended Energy (kcal/kg/day)[1]

Weight, g	Week 1	Week 2	Both Weeks
Overall	77.4 (22.1) 75.7 (61.5 - 93.4)	100.4 (26.8) 94.9 (80.2 - 114.5)	89.0 (27.1) 87.3 (71.7 - 104.9)
501 - 700	70.1 (21.5) 69.0 (56.6 - 83.2)	95.2 (24.1) 93.0 (76.8 - 106.6)	82.7 (26.1) 81.7 (65.9 - 97.0)
701 - 900	73.4 (18.5) 75.3 (58.9 - 86.7)	94.0 (25.1) 87.4 (76.6 - 106.2)	83.7 (24.3) 82.3 (67.7 - 95.2)
901 - 1200	86.1 (21.6) 86.9 (70.7 - 105.1)	109.5 (27.6) 104.6 (92.5 - 124.1)	97.8 (27.4) 97.4 (78.2 - 109.9)
1201 - 1500	101.9 (17.7) 107.1 (99.2 - 107.9)	124.0 (34.3) 137.3 (78.1 - 139.1)	112.9 (28.7) 107.1(99.2 - 137.3)

[1] Values are means (±*SD*); medians, (25th percentile - 75th percentile)

Actual/Delivered Energy (kcal/kg/day)[1]

Weight, g	Week 1	Week 2	Both Weeks
Overall	65.3 (22.3) 64.9 (48.2 - 80.7)	86.1 (20.5) 85.8 (71.5 - 101.5)	75.7 (23.8) 75.9 (58.9 - 92.7)
501 - 700	58.9 (19.1) 59.2 (47.1 - 71.4)	81.0 (21.2) 80.4 (69.0 - 94.2)	70.0 (22.5) 70.0 (55.3 - 85.9)
701 - 900	60.8 (18.5) 59.3 (47.5 - 76.1)	81.3 (18.9) 80.3 (68.8 - 95.5)	71.0 (21.3) 70.9 (54.8 - 82.8)
901 - 1200	73.4 (23.4) 73.4 (54.2 - 96.7)	94.5 (19.7) 96.4 (80.1 - 110.6)	83.9 (24.1) 85.6 (68.2 - 101.0)
1201 - 1500	92.6 (30.6) 100.1 (75.1 - 119.0)	92.4 (20.2 103.4 (74.7 - 110.7)	92.5 (24.9) 101.8 (75.1 - 110.7)

[1] Values are means (±*SD*); medians, (25th percentile - 75th percentile)

Prescribed/Intended Protein (g/kg/day)[1]

Weight, g	Week 1	Week 2	Both Weeks
Overall	3.7 (0.6) 3.5 (3.5 - 4.1)	4.1 (0.8) 4.0 (3.5 - 4.5)	3.9 (0.7) 3.8 (3.5 - 4.3)
501 - 700	3.5 (0.7) 3.5 (3.2 - 4.0)	4.1 (0.8) 4.0 (3.5 - 4.3)	3.8 (0.8) 3.8 (3.5 - 4.2)
701 - 900	3.7 (0.6) 3.5 (3.2 - 4.3)	4.1 (0.6) 4.0 (3.8 - 4.6)	3.9 (0.6) 3.9 (3.5 - 4.3)
901 - 1200	3.8 (0.6) 3.8 (3.5 - 4.2)	4.2 (0.9) 4.2 (3.9 - 4.5)	4.0 (0.8) 4.0 (3.5 - 4.3)
1201 - 1500	3.9 (0.3) 3.8 (3.8 - 3.8)	4.7 (1.0) 4.9 (3.5 - 4.9)	4.3 (0.8) 3.8 (3.8 - 4.9)

[1] Values are means (±*SD*); medians, (25th percentile - 75th percentile)

Actual/Delivered Protein (g/kg/day)[1]

Weight, g	Week 1	Week 2	Both Weeks
Overall	3.1 (0.7) 3.1 (2.7 - 3.6)	3.6 (0.8) 3.7 (3.2 - 4.0)	3.3 (0.8) 3.4 (2.9 - 3.9)
501 - 700	3.0 (0.7) 3.0 (2.6 - 3.5)	3.5 (0.7) 3.6 (3.1 - 4.0)	3.3 (0.8) 3.3 (2.8 - 3.8)
701 - 900	3.1 (0.8) 3.0 (2.5 - 3.7)	3.5 (0.8) 3.7 (3.2 - 4.0)	3.3 (0.8) 3.4 (2.8 - 3.9)
901 - 1200	3.3 (0.7) 3.2 (2.9 - 3.7)	3.6 (0.8) 3.7 (3.3 - 4.1)	3.4 (0.7) 3.5 (3.1 - 4.0)
1201 - 1500	3.7 (0.7) 3.5 (2.9 - 4.3)	3.5 (0.5) 3.5 (3.3 - 4.0)	3.6 (0.6) 3.5 (3.3 - 4.1)

[1] Values are means (±*SD*); medians, (25^{th} percentile - 75^{th} percentile)

APPENDIX F

Statistical Analysis for the mean protein intakes ±*SD* and minimum - maximum as a percent of theoretical estimates of protein requirements (Ziegler's guidelines) of VLBW infants during the first 14 days of life, week 1, week 2 and both weeks. Percentage was calculated as prescribed/intended (P/I) or actual/delivered (A/D) protein intakes divided by theoretical estimates of protein requirements.

Time Period (Day of Life)	Percent of P/I Protein Mean (±*SD*) Min - Max	*p*-value, Percent of P/I Protein	Percent of A/D Protein Mean (±*SD*) Min - Max	*p*-value, Percent of A/D Protein
1	86.69 (21.91) 0 - 106.42	0.0005*	76.39 (14.23) 27.84 - 94.63	< 0.0001*
2	96.89 (18.67) 0 - 122.91	0.3044	77.03 (19.88) 23.69 - 117.22	< 0.0001*
3	104.28 (11.32) 85.71 - 125.73	0.0235	84.94 (20.09) 28.37 - 123.28	< 0.0001*
4	106.57 (12.54) 72.65 - 131.79	0.0020	88.11 (20.01) 45.75 - 124.74	0.0006*
5	111.44 (13.10) 80.00 - 131.79	< 0.0001*	97.16 (15.55) 50.44 - 120.62	0.2547
6	112.17 (12.67) 85.71 - 136.28	< 0.0001*	96.61 (19.44) 53.76 - 123.83	0.2771
7	115.77 (14.38) 85.71 - 152.91	< 0.0001*	103.01 (16.27) 63.01 - 136.25	0.2496
8	117.65 (14.69) 88.15 - 161.73	< 0.0001*	102.39 (22.31) 19.41 - 142.48	0.5016
9	118.26 (14.62) 92.77 - 149.29	< 0.0001*	103.06 (18.41) 57.15 - 137.61	0.2992
10	117.01 (20.48) 40.76 - 172.60	< 0.0001*	101.58 (20.72) 35.33 - 131.02	0.6325
11	119.00 (21.96) 85.71 - 187.26	< 0.0001*	103.81 (24.77) 35.50 - 153.69	0.3363
12	120.06 (25.24) 80.60 - 187.91	< 0.0001*	99.81 (22.06) 24.49 - 147.57	0.9578
13	116.76 (24.87) 66.91 - 189.91	0.0001*	101.74 (19.54) 21.43 - 141.31	0.5758
14	118.05 (31.79) 34.12 - 195.96	0.0009*	100.50 (23.92) 29.85 - 141.45	0.8950
Week 1 (days 1 - 7)	104.92 (17.82) 0 - 152.91	< 0.0001*	89.28 (20.27) 23.69 - 136.25	< 0.0001*
Week 2 (days 8 - 14)	118.11 (22.45) 34.12 - 195.96	< 0.0001*	101.85 (21.58) 19.41 - 153.69	0.1531
Overall (days 1 - 14)	111.55 (21.31) 0 - 195.96	< 0.0001*	95.62 (21.85) 19.41 - 153.69	< 0.0001*

[1] Percent of P/I and A/D values were calculated compared to Ziegler's theoretical estimated protein requirements.

* Indicates a significant difference at a Bonferroni adjusted alpha level of 0.05 (adjusted *p*-value = 0.0015), for a one-sided t-test, with a null hypothesis that the percentage is 100. Percentage was calculated as P/I or A/D divided by Ziegler's theoretical estimated protein requirement.

APPENDIX G

Statistical Analysis for the mean protein intakes ±*SD* and minimum - maximum as g/kg/day compared to theoretical estimates of protein requirements (Ziegler's guidelines) of VLBW infants during the first 14 days of life, week 1, week 2 and both weeks. Differences in protein intakes were calculated as theoretical estimates minus prescribed/intended (P/I) or actual/delivered (A/D) intakes.

Time Period (Day of Life)	Theoretical Estimated Protein Minus P/I Protein[1] Mean (±*SD*) Min - Max	*p*-value, Theoretical Estimated Protein Minus P/I	Theoretical Estimated Protein Minus A/D Protein[1] Mean (±*SD*) Min - Max	*p*-value, Theoretical Estimated Protein Minus A/D
1	0.47 (0.77) -0.22 - 3.50	0.0005*	0.83 (0.50) 0.19 - 2.53	< 0.0001*
2	0.11 (0.65) -0.80 - 3.50	0.3021	0.80 (0.70) -0.60 - 2.67	< 0.0001*
3	-0.15 (0.39) -0.87 - 0.50	0.0237	0.53 (0.70) -0.81 - 2.51	< 0.0001*
4	-0.23 (0.44) -1.11 - 0.96	0.0020	0.42 (0.70) -0.85 - 1.90	0.0005*
5	-0.40 (0.46) -1.11 - 0.70	< 0.0001*	0.10 (0.54) -0.72 - 1.73	0.2518
6	-0.43 (0.44) -1.27 - 0.50	< 0.0001*	0.12 (0.68) -0.83 - 1.62	0.2749
7	-0.55 (0.50) -1.85 - 0.50	< 0.0001*	-0.11 (0.57) -1.27 - 1.29	0.2505
8	-0.62 (0.51) -2.16 - 0.41	< 0.0001*	-0.08 (0.78) -1.49 - 2.82	0.5041
9	-0.64 (0.51) -1.73 - 0.25	< 0.0001*	-0.11 (0.64) -1.32 - 1.50	0.3049
10	-0.59 (0.71) -2.47 - 2.01	< 0.0001*	-0.06 (0.72) -1.06 - 2.20	0.6271
11	-0.66 (0.76) -2.97 - 0.50	< 0.0001*	-0.13 (0.86) -1.88 - 2.26	0.3397
12	-0.70 (0.88) -3.08 - 0.66	< 0.0001*	0.01 (0.77) -1.66 - 2.64	0.9594
13	-0.59 (0.87) -3.15 - 1.16	0.0001*	-0.06 (0.68) -1.45 - 2.75	0.5722
14	-0.63 (1.11) -3.36 - 2.31	0.0009*	-0.02 (0.84) -1.45 - 2.46	0.8919
Week 1 (days 1 - 7)	-0.17 (0.62) -1.85 - 3.50	< 0.0001*	0.38 (0.71) -1.27 - 2.67	< 0.0001*
Week 2 (days 8 - 14)	-0.63 (0.78) -3.36 - 2.31	< 0.0001*	-0.06 (0.75) -1.88 - 2.82	0.1537
Overall (days 1 - 14)	-0.40 (0.74) -3.36 - 3.50	< 0.0001*	0.15 (0.76) -1.88 - 2.82	< 0.0001*

[1] Differences were calculated as Ziegler's theoretical estimated protein requirements minus the P/I or actual A/D intakes.

* Indicates a significant difference at a Bonferroni adjusted alpha level of 0.05 (adjusted *p*-value = 0.0015), for a two-sided t-test, with a null hypothesis that the difference is 0.

APPENDIX H

Correlation analysis for days of life (DOL) until first full enteral nutrition (100 kcal/kg/day) with mean actual/delivered (A/D) energy intakes and the mean actual/delivered (A/D) protein intakes during the first week of life.

Weight, g	Correlation with Mean A/D Energy for DOLs 1 - 7 (kcal/kg/day)	Correlation with Mean A/D Protein for DOLs 1 - 7 (kcal/kg/day)
Overall (n = 38)[1]		
- Pearson Coefficient	-0.3220	-0.0699
- *p*-value	0.0456*	0.6725
501 - 700 (n = 14)[1]		
- Pearson Coefficient	-0.4153	-0.2939
- *p*-value	0.1397	0.3077
701 - 900 (n = 9)		
- Pearson Coefficient	-0.3135	0.0169
- *p*-value	0.4114	0.9655
901 - 1200 (n = 14)		
- Pearson Coefficient	-0.3145	0.3430
- *p*-value	0.2735	0.2300
1201 - 1500 (n = 1)		
- Pearson Coefficient	N/A	N/A
- *p*-value	N/A	N/A

Abbreviations: N/A = not applicable

[1] One infant in the 501 - 700 g group missed day 1; a second infant in the 500 - 701 g group missed days 1 and 2

* Indicates a significant difference at a Bonferroni adjusted alpha level of 0.05 (adjusted *p*-value = 0.0015), for a one-sided t-test, with a null hypothesis that the actual energy or protein would reach full enteral nutrition (100 kcal/kg/day).

APPENDIX I

Growth milestones for VLBW infants (n = 40) within birth weight categories and appropriateness for gestational age (appropriate for gestational age or small for gestational age) categories.

Fenton Growth Grid (Appropriate for Gestational Age)

Birth Weight Percentile	Weight Categories, g				
	501-700	701-900	901-1200	1201-1500	Total
< 3rd percentile	0	0	0	0	0
3-10th percentile	0	0	0	0	0
10-50th percentile	6	4	7	1	18
50-90th percentile	4	4	4	0	12
90-97th percentile	0	0	0	0	0
Total	10	8	11	1	30

Fenton Growth Grid for Day of Life RTBW (Appropriate for Gestational Age)

Weight Percentile	Weight Categories, g				
	501-700	701-900	901-1200	1201-1500	Total
< 3rd percentile	0	0	0	0	0
3-10th percentile	2	0	3	1	6
10-50th percentile	8	8	8	0	24
50-90th percentile	0	0	0	0	0
90-97th percentile	0	0	0	0	0
Total	10	8	11	1	30

Fenton Growth Grid at 36 Weeks' PMA (Appropriate for Gestational Age)

Weight Percentile	Weight Categories, g				
	501-700	701-900	901-1200	1201-1500	Total
< 3rd percentile	1	0	1	0	2
3-10th percentile	0	1	5	1	7
10-50th percentile	6	4	4	0	14
50-90th percentile	0	0	1	0	1
90-97th percentile	0	0	0	0	0
< 36 weeks	3	3	0	0	6
Total	10	8	11	1	30

Lubchenco Growth Grid at 36 Weeks' PMA (Appropriate for Gestational Age)

Weight Percentile	Weight Categories, g				
	501-700	701-900	901-1200	1201-1500	Total
< 10th percentile	1	1	2	0	4
10-25th percentile	1	0	3	1	5
25-50th percentile	4	3	5	0	12
50-75th percentile	1	1	1	0	3
< 36 weeks	3	3	0	0	6
Total	10	8	11	1	30

Olsen Growth Grid at 36 Weeks' PMA (Appropriate for Gestational Age)

Weight Percentile	Weight Categories, g				
	501-700	701-900	901-1200	1201-1500	Total
< 3rd percentile	1	0	1	0	2
3rd-10th percentile	0	1	2	0	3
10-25th percentile	3	1	7	1	12
25-50th percentile	3	2	0	0	5
50-75th percentile	0	1	1	0	2
< 36 weeks	3	3	0	0	6
Total	10	8	11	0	30

Fenton Growth Grid (Small for Gestational Age)

Birth Weight Percentile	Weight Categories, g				
	501 700	701-900	901-1200	1201-1500	Total
< 3rd percentile	1	0	0	0	1
3-10th percentile	5	3	0	0	8
10-50th percentile	0	0	0	1	1
50-90th percentile	0	0	0	0	0
90-97th percentile	0	0	0	0	0
Total	6	3	0	1	10

Fenton Growth Grid for Day of Life RTBW (Small for Gestational Age)

Weight Percentile	Weight Categories, g				
	501-700	701-900	901-1200	1201-1500	Total
< 3rd percentile	3	1	0	0	4
3-10th percentile	3	0	3	0	6
10-50th percentile	0	0	0	0	0
50-90th percentile	0	0	0	0	0
90-97th percentile	0	0	0	0	0
Total	6	1	3	0	10

Fenton Growth Grid at 36 Weeks' PMA (Small for Gestational Age)

	Weight Categories, g				
Weight Percentile	501-700	701-900	901-1200	1201-1500	Total
< 3rd percentile	3	0	1	0	4
3-10th percentile	2	1	2	0	5
10-50th percentile	1	0	0	0	1
50-90th percentile	0	0	0	0	0
90-97th percentile	0	0	0	0	0
Total	6	1	3	0	10

Lubchenco Growth Grid at 36 Weeks' PMA (Small for Gestational Age)

Weight Percentile	Weight Categories, g				
	501-700	701-900	901-1200	1201-1500	Total
< 10th percentile	4	1	2	0	7
10-25th percentile	1	0	1	0	2
25-50th percentile	1	0	0	0	1
50-75th percentile	0	0	0	0	0
Total	6	1	3	0	10

Olsen Growth Grid at 36 Weeks' PMA (Small for Gestational Age)

Weight Percentile	Weight Categories, g				
	501-700	701-900	901-1200	1201-1500	Total
< 3rd percentile	2	0	0	0	2
3rd-10th percentile	2	1	2	0	5
10-25th percentile	1	0	1	0	2
25-50th percentile	1	0	0	0	1
50-75th percentile	0	0	0	0	0
Total	5	1	3	0	10

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CURRICULUM VITAE

Deborah Marie Abel

Education:

2012 — Indiana University
Indiana-Purdue University, Indianapolis
Indianapolis, IN
- PhD in Health and Rehabilitation Sciences
- Minor in Pediatric Nutrition

2003 — Indiana University
Indianapolis, IN
- Pediatric Nutrition Fellowship, six-month Certificate Program (completed)

1990 — Indiana University of Pennsylvania
Indiana, PA
- Master of Science, Food and Nutrition

1978 — Indiana University of Pennsylvania
Indiana, PA
- Bachelor of Science, Dietetics

Honors, Awards:

2012 — TK Carl Promise Award for Academic Excellence and Professional Promise, Indiana University, School of Health and Rehabilitation Sciences, Indiana-Purdue University, Indianapolis, IN

2004 — Louise Irwin Scholarship Award for Graduate Studies, Nutrition and Dietetics Department, Indiana University, School of Health and Rehabilitation Sciences, Indiana-Purdue University, Indianapolis, IN

Professional Experience:

1/08 - Current — Visiting Lecturer of Nutrition & Dietetics
Nutrition and Dietetic, School of Rehabilitation and Health Sciences, Indiana University, Indianapolis, IN
- Teaching Responsibilities for the e-Learning certificate program:
  IN SHRS N570 17758 Pediatric Nutrition I
  IN SHRS N572 8414 Advanced Pediatric Nutrition
  IN SHRS N574 8415 Nutrition Management High Risk Neonate/Infants

- Coordinator, Leadership Education in MCH Nutrition

(Pediatric Focus)
Responsible for coordinating preceptors and learning experiences for the Pediatric Nutrition Fellowship at Riley Hospital for Children, IU Health.

8/03 - 12/07 Teaching Assistant for Dr. Rickard and Dr. Brady
Nutrition and Dietetic, School of Rehabilitation and Health Sciences, Indiana University, Indianapolis, IN

- Assisted with the development of an e-Learning certificate program that allows nutrition students to take pediatric nutrition classes on-line
- Completed literature reviews on a variety of pediatric nutrition topics including the NICU (Newborn Intensive Care Unit)
- Assisted with the development of e-Learning leadership courses
- Developed the "Leadership in Action" component in the Family Centered Care Module; a module in the Advanced Pediatric Nutrition Course
- Under the direction of Dr. Brady, developed the NICU course; completed literature review, created innovative group activities to assist learning complicated materials, obtained national speakers and assisted with technology of placing presentations on-line.

8/03 - Current Pediatric-Neonatal Clinical Dietitian
Riley Hospital for Children, Indianapolis, IN

- Complete nutritional assessments of high-risk infants in the newborn intensive care unit (NICU)
- Write and make feeding and nutrition recommendations on hyperalimentation and enteral feedings
- Problem solve complicated nutrition management of high-risk infants in the NICU
- Teach current feeding and nutrition practices to residents, nurse practitioners, and other disciplines in the NICU
- Work with Principle Investigators and their research projects that concern nutrition management to improve the care of high-risk infants in the NICU
- Developed the Nutrition Electronic Assessment Tool (NEAT) Computerized tool that completes calorie counts and growth analysis of high-risk infants in the NICU

5/02 - 5/03 Clinical Dietitian and Food Service Manager
Valle Vista Behavioral Health System, Greenwood, IN

- Completed nutrition assessments and education of all pediatric, adolescent, and adult population
- Reduced department expense budget by 14% in First Quarter of 2003; savings of $16,018
- Increased Department Net Revenue budget by 8% First Quarter of 2003

- Negotiated and implemented all new equipment in the kitchen

01/02 - 3/02 Clinical Dietitian
Sister of St. Francis Health System, Inc. Beech Grove, IN
- Temporary position for maternity leave
- Completed nutrition assessments and education for cardiac patients

06/97 - 12/00 Food Service Manager
Columbus Regional Hospital, Columbus, IN
- Successfully demonstrated growth in meal production by increase of 109,523 meals
- Increase in cafeteria sales by $220,410 in 1998 versus 1997
- Increase Press Ganey score "meal ratings" of 4.7 improvement in 1998 versus 1997 (The quarter I left the Press Ganey went to the 98%tile)
- Department honors received in 1998 are "Best of the Midwest" picked as the best eating establishment in the mid-west

9/96 - 6/97 Patient Service Manager
Memorial Hospital of South Bend, South Bend, IN
- Resolved employee union conflicts
- Implemented nutrition screening form

11/94 - 9/96 Nutrition Service Manager
ARAMARK, Inc., Lakeland Regional Health System, St. Joseph, MI
- Eliminated 30 FTE's through restructuring of kitchen and clinical nutrition staff without layoff's system-wide (multi-sites)
- Co-led a team that developed a state of the art kitchen
- Developed Nutrition Nursing Task Force within hospitals, thus enabling them to solve problems internally

2/93 - 11/94 Assistant Director of Nutrition Services
ARAMARK, Inc., Park Medical Center, Columbus, OH
- Passed JCAHO with Accreditation with accommodations, special mention of food service accomplishments
- Negotiated a contract with local prison hospital's clinical and food service department which generated a revenue of $20,000 annually for Park Medical Center

10/90 - 2/93 Clinical Dietitian
ARAMARK, Inc., Western Psychiatric Hospital, Pittsburgh, PA
- Co-authored publication in The Journal of Clinical Psychiatry with a physician

- Completed nutritional assessments and education for pediatric, geriatric and eating disorder population

2/89 - 10/90 President
HEARTWISE, Pittsburgh, PA

- Created and published counselor 250-page nutrition manual/employee handbook
- These publications assisted professional nutritionists in counseling clients who have experience cardiovascular disease, who are at high risk for heart disease, or who are interested in cardiovascular fitness and disease prevention

5/80 - 8/89 Nutrition Manager
Women, Infant, and Children Program, Pittsburgh, PA

- Responsibility included implementation of the program - first time in county

Patents:

US Patent 7,909,763, Neonatal nutrition assessment system, Deborah M. Abel, March 22, 2011.

Publications:

"Parenteral nutrition-associated cholestasis in VLBW infants". In: Adamkin, DH. Nutritional Strategies for the Very Low Birthweight Infant. Cambridge, United Kingdom: Cambridge University Press; 2009, Chapter 11.

"Nutritional management of preterm infants with short bowel syndrome". In: Adamkin, DH. Nutritional Strategies for the Very Low Birthweight Infant. Cambridge, United Kingdom: Cambridge University Press; 2009, Chapter 26.

Presentations:

2000 - 2005	Invited Presenter, “Overcoming Negative Emotions” at Right Management to a group of top executives who were outsourced, yearly for five years.
2000 - present	Leadership Council and Advisor, “Camp About Face” for children and young adults with craniofacial anomalies; specifically, provided counsel, advising and leadership for the development of character and leadership qualities, yearly.
2005 - 2010	Enteral and parenteral nutrition power point presentations to nurse practitioner students and residents at Riley Hospital and surrounding hospitals, twice a month.
2008	Food and Nutrition Conference and Exhibition, Chicago, IL, October 2008; Plenary Presentation “Family Centered Care and Nutrition: Who is in Charge?”
2011	National Perinatal Association Conference, Louisville, KY, October 2011; Plenary Presentation “Malnutrition, Micronutrient Deficiency and the Relationship to Perinatal Infection”.
2011	National Perinatal Association Conference, Louisville, KY, October 2011; Invited Speaker for Pre-Conference Presentation “Human Milk: The Best Medicine for Preterm Infants - Do We need Fortification?”